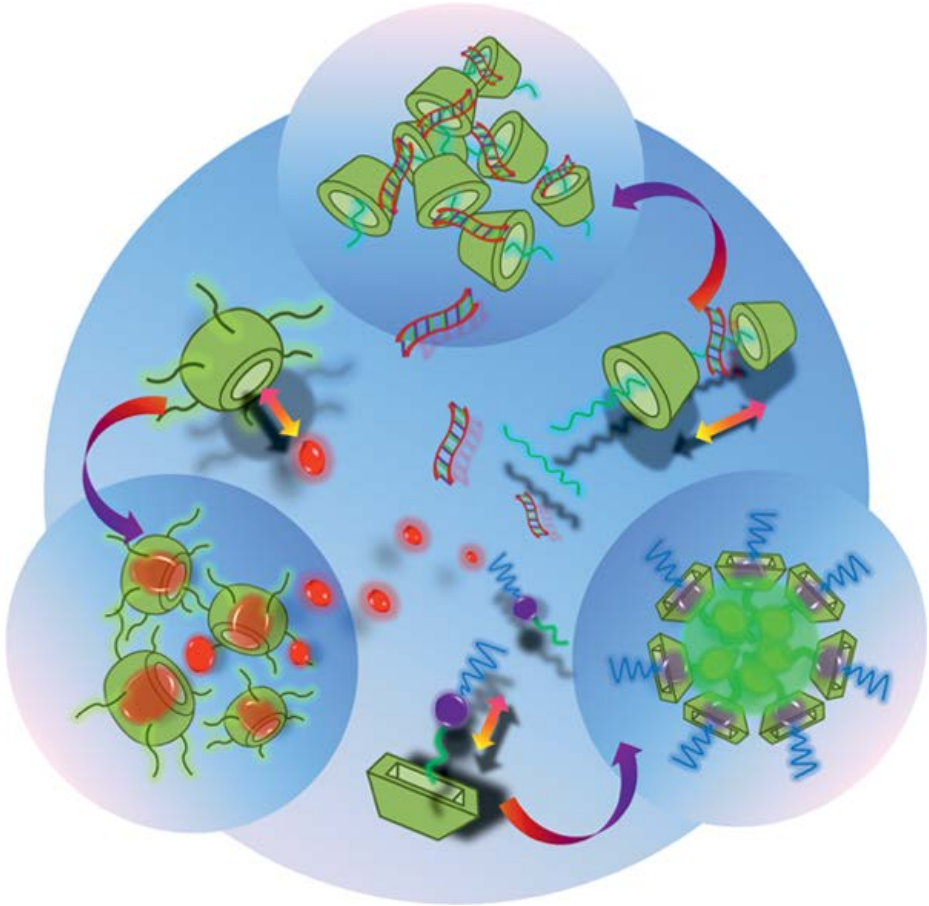
به نام آنکه جان را فکرت آموخت

چراغ دل به نور جان برافروخت

Cyclodextrins in Pharmaceutical Sciences



Supervisor: Dr. R. Hosseinzadeh

By: Javid Jahanfar --- NOV. 2018

Cyclodextrins in Pharmaceutical Sciences

Supramolecular Pharmaceutical Sciences: A Novel Concept Combining Pharmaceutical Sciences and Supramolecular Chemistry with a Focus on Cyclodextrin-Based Supermolecules

Taishi Higashi, Daisuke Iohara, Keiichi Motoyama, Hidetoshi Arima

Supramolecular affinity between a drug guest and a macrocyclic host

Introduction

- Supramolecular chemistry, characterized by the use of specific, directional, tunable, and reversible molecular recognition motifs, has been demonstrated as a useful strategy to prepare controlled and predictable materials organized across length scales. In the context of their use as medical devices or therapeutics, this has led to the expanding research area of supramolecular biomaterials. A significant benefit realized in leveraging supramolecular chemistry for the design of biomaterials is that their properties often follow directly from those of their molecular-level building blocks; namely, **properties that are predictable, reversible, and highly tunable.**
- Additional functional benefit also arises from the combinatorial modularity of supramolecular interactions, as the strong affinity of a specific supramolecular motif enables diverse modification of the molecule away from the motif while maintaining the basic interaction.
- In the pharmaceutical field, supermolecules such as liposomes, micelles, nanoparticles, hydrogels, nanogels, and inclusion complexes are widely used.
- Recently, an emphasis has been placed on strategies which facilitate so-called ‘‘precision medicine’’ in the tailoring of disease treatment or prevention strategies to a specific patient. This approach takes into account variabilities presented in disease, genetics, lifestyle, or environment of the patient in designing an ‘‘optimized’’ treatment. Such an approach has been fueled in large part by expanding capabilities in genomics and proteomics.

Ref: 1,2

Introduction

- Drug delivery may offer useful tools in the context of precision medicine, specifically if a drug carrier can be designed and tailored to ***facilitate tuning of drug dosage, drug selection/combination, or drug kinetics/availability at the point-of-care.***
- In the context of therapy, one could envision this to allow patient-specific "mix-and-match" function to be introduced. Also, using supramolecular design in order to create systems that are stimuli-responsive provides great utility.
- In the field of drug delivery, strategies which can accomplish some or all of the following are needed:

1- improved therapeutic efficacy

2- reduced off-site drug exposure/toxicity

3- reduced administered dose or dosing frequency

4- improved therapeutic adherence

5- patient-specific therapeutic function

Ref: 1,2

Supramolecular affinity between a drug guest and a macrocyclic host

- The first application of supramolecular chemistry in the field of drug delivery was brought to bear with macrocyclic host molecules used as excipients, solubility enhancers, and drug carriers. In general, supramolecular host–guest interactions arise from a macrocycle host (often referred to as a cavitand) accommodating some guest molecule within its portal.
- In the context of drug delivery, these interactions typically occur in aqueous environments (e.g., formulation or body), and as such comprises a macrocycle host with a hydrophilic outer shell and a hydrophobic cavity accommodating a hydrophobic drug molecule.
- Certain macrocycles introduce an additional enthalpic driving force for host–guest complexation through the formation of hydrogen bonds between proton-donating guests and proton accepting groups on the macrocycle.

Ref: 1,2

Supramolecular affinity between a drug guest and a macrocyclic host

The specific biomedical applications of the host−guest systems Discussed contain several leading directions, that is,

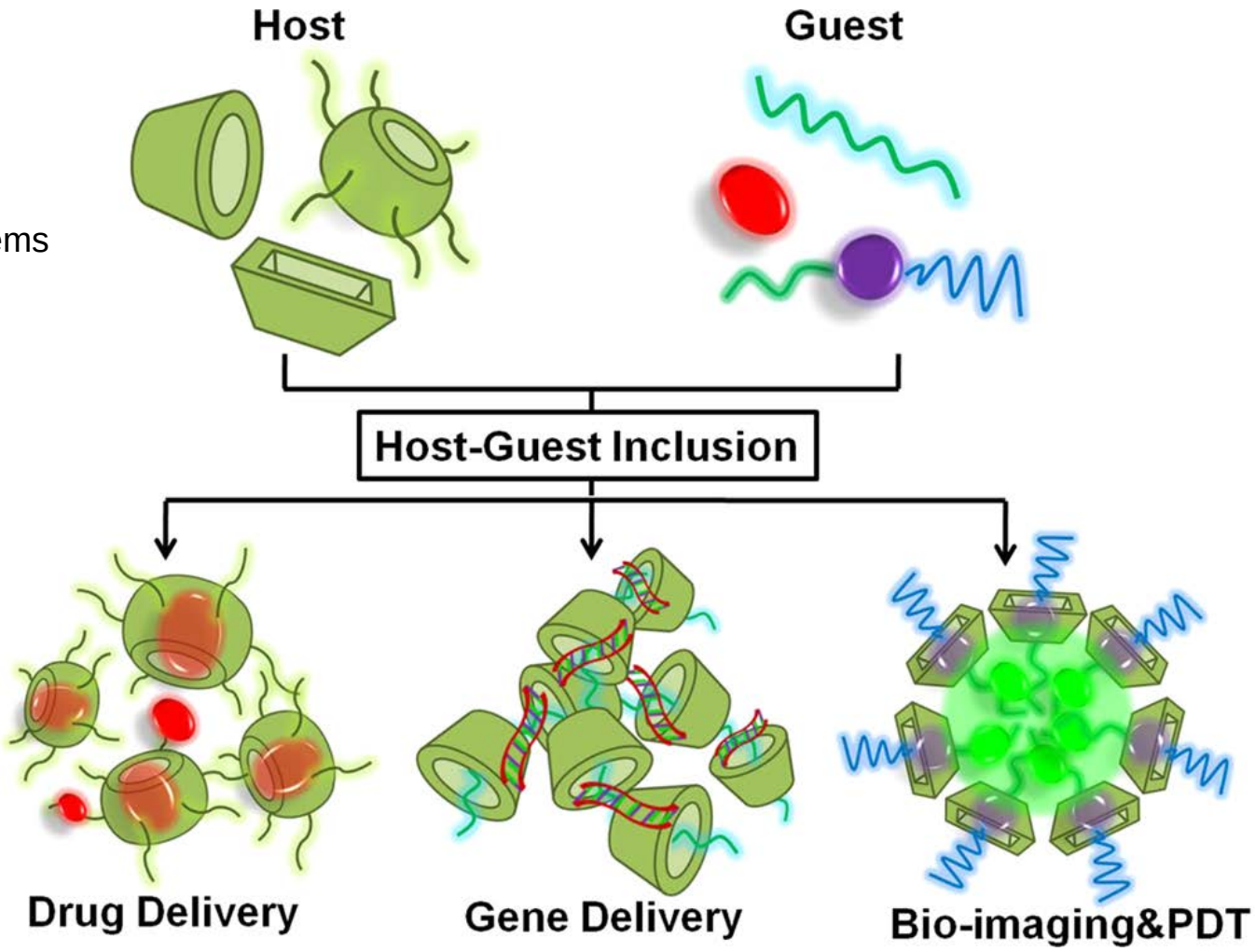
drug delivery

Gene delivery

drug/gene codelivery

bioimaging

photodynamic therapy (PDT)



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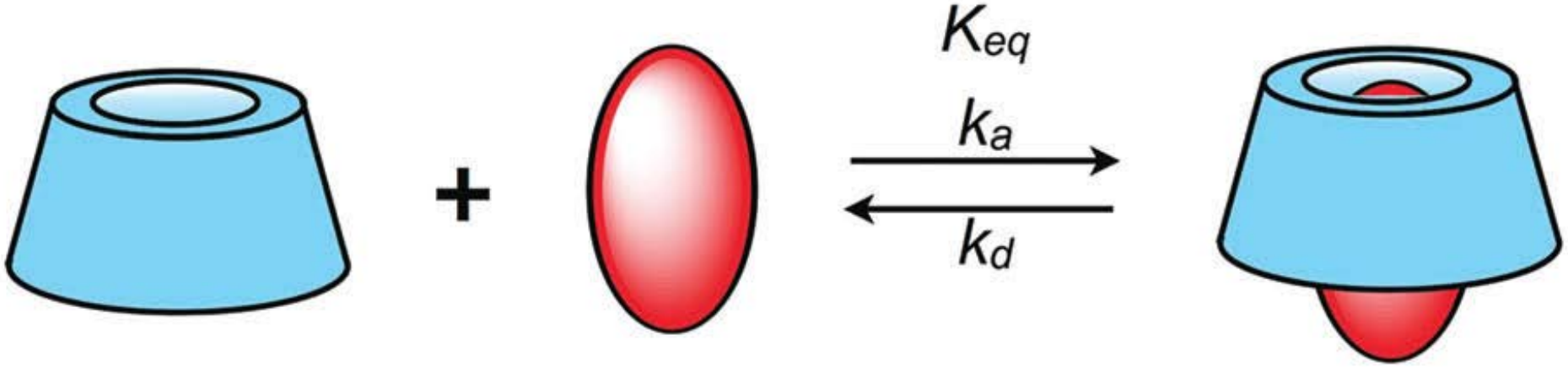
Supramolecular affinity between a drug guest and a macrocyclic host

- The vast majority of host–guest supramolecular interactions exist at thermodynamic equilibrium (global free energy minimum) with host–guest stoichiometry of 1 : 1, and are defined by a characteristic equilibrium binding constant (Keq) along with rate constants of association (ka) and dissociation (kd). The rate constant ka, understood as the ‘‘on rate’’ of the interaction, can be approximated to be diffusion limited for most host–guest interactions.



Ref: 2

Drug delivery by inclusion in supramolecular macrocycles

➢ pillar[n]arenes and Calix[n]arenes

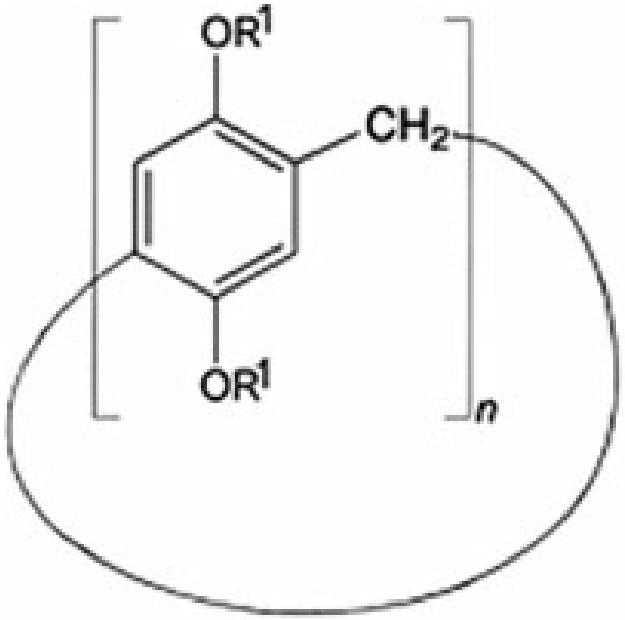
Though more limited in their use for drug delivery at this point, other classes of supramolecular macrocycles, including pillar[n]arenes and calix[n]arenes, have possible application in the context of drug encapsulation and for use as solubility enhancers. For example, a water soluble pillar[5]arene was demonstrated as a useful carrier for an antibiotic drug. Calix[n]arenes and pillar[n]arenes may also have use as excipients in the formulation of protein drugs. Importantly, in comparison to Cyclodextrin and CB[n] macrocycles, the chemical design space for these macrocycles is very broad, as the faces of the molecules can be modified asymmetrically. This enables the creation of macrocycles with functionalized units on one side as well as very deep cavitands, both of which could lead to eventual application in drug delivery, especially in cases where a very large drug may need to be encapsulated to promote solubility.

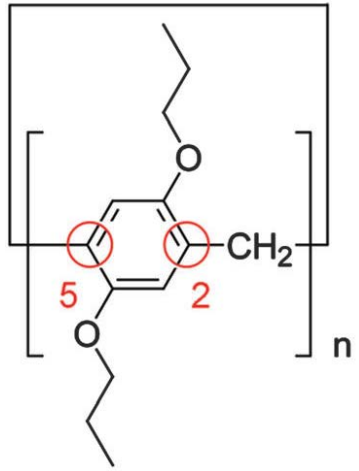
In spite of the synthetic benefit that may be realized from water soluble variants of the pillar[n]arene and calix[n]arene families of macrocycles, they have not been significantly explored in the formulation of a drug guest to the extent of cyclodextrin or even curcubit[n]urils.

Ref: 2

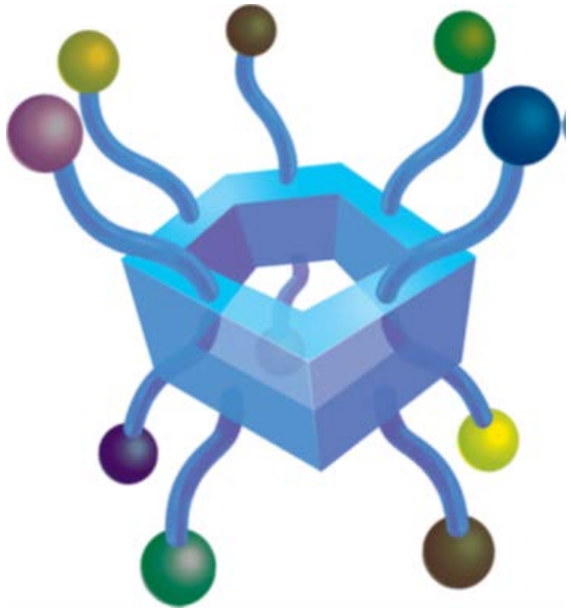
Drug delivery by inclusion in supramolecular macrocycles

➢ pillar[n]arenes





n = 5 (**H1**)
n = 6 (**H2**)

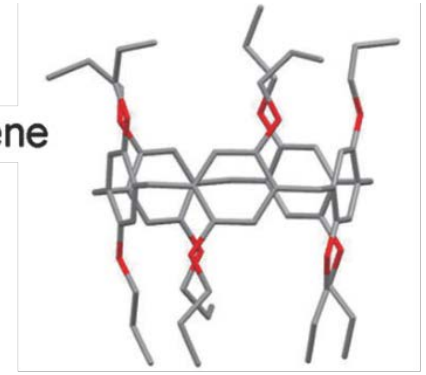


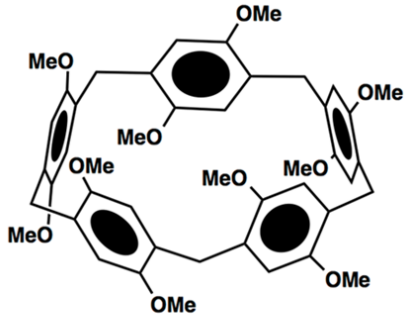
Ref: 4, 5, 6

Drug delivery by inclusion in supramolecular macrocycles

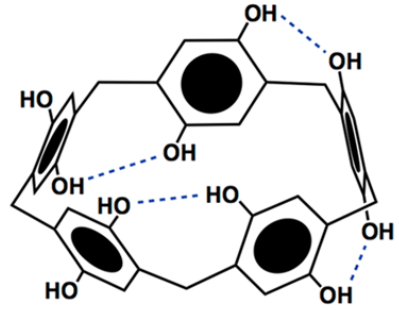
pillar[n]arenes

Pillar[5]arene



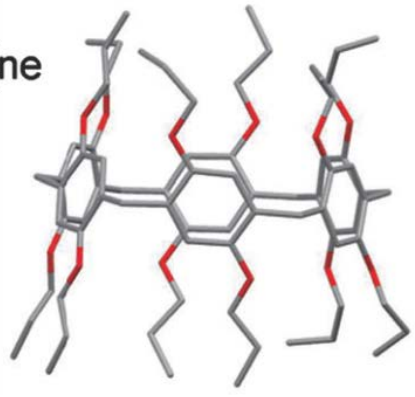


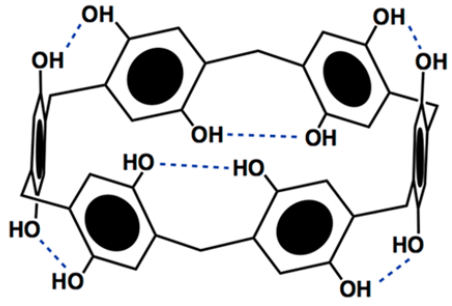
DMpillar[5]arene



Pillar[5]arene

Pillar[6]arene



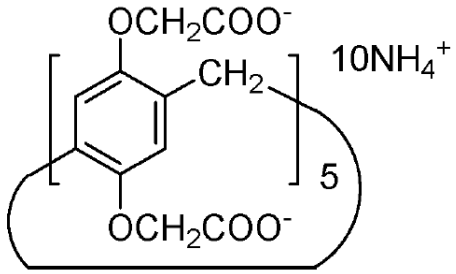


Pillar[6]arene

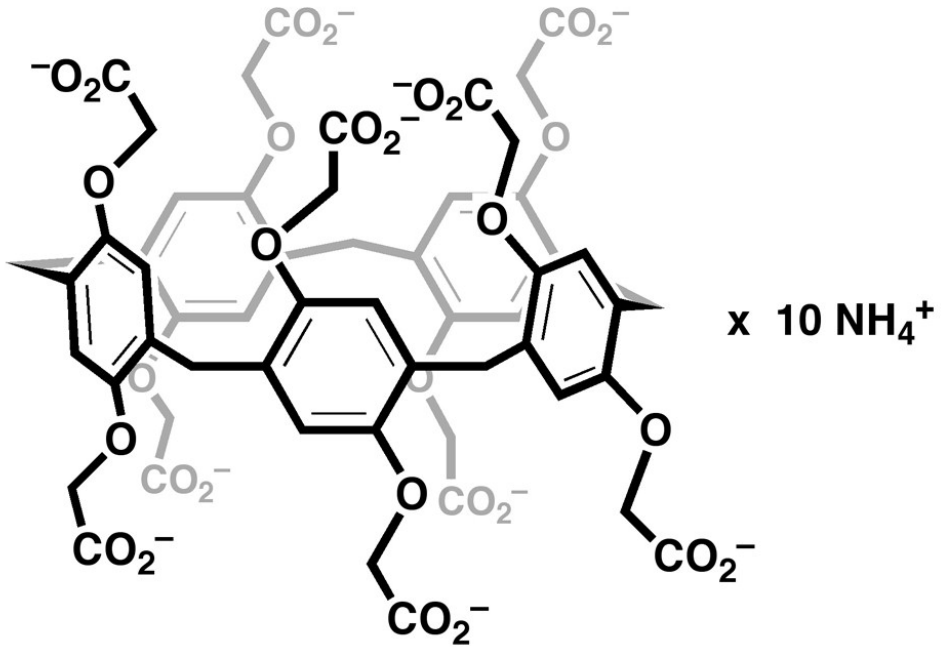
Ref: 4, 5

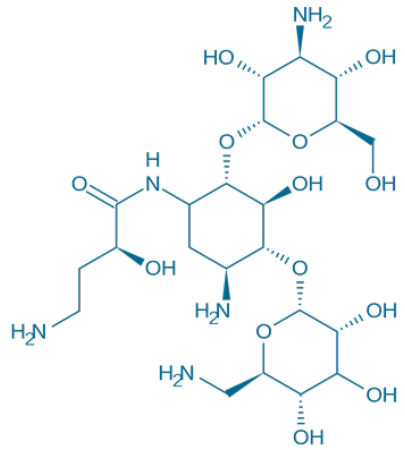
Drug delivery by inclusion in supramolecular macrocycles

pillar[n]arenes



Water-soluble pillar[5]arene



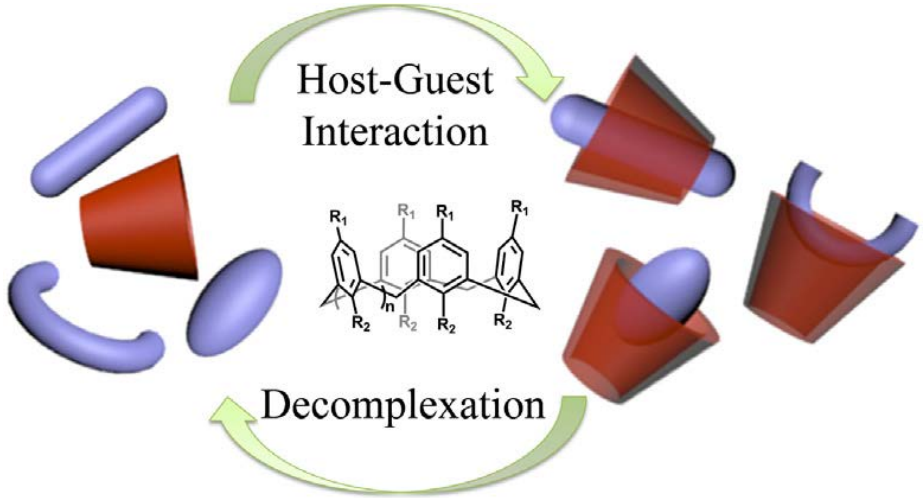


amikacin

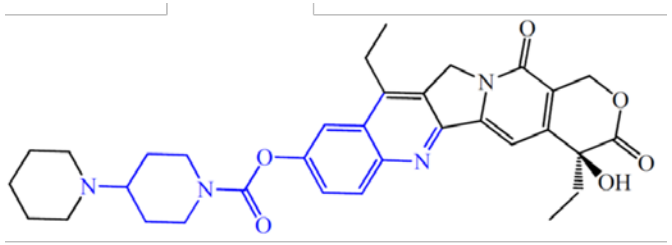
Ref: 5, 6, 30

Drug delivery by inclusion in supramolecular macrocycles

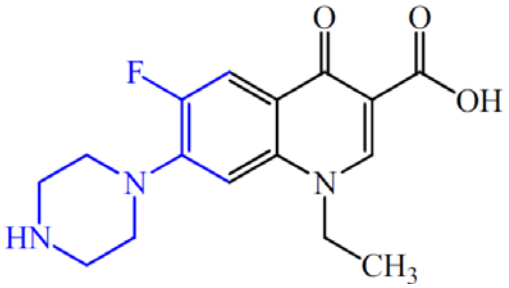
calix[n]arene



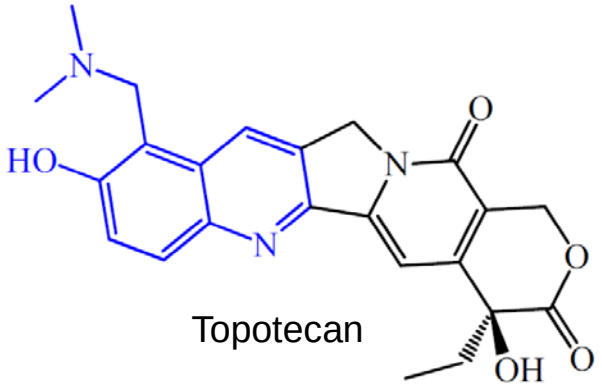
		R_1, R_2
Calixarene	Drugs	Functional Groups



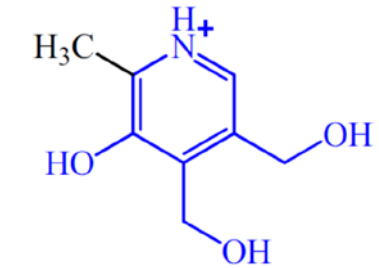
Irinotecan



Norfloxacin



Topotecan



Vitamin B_6

Ref: 7, 8

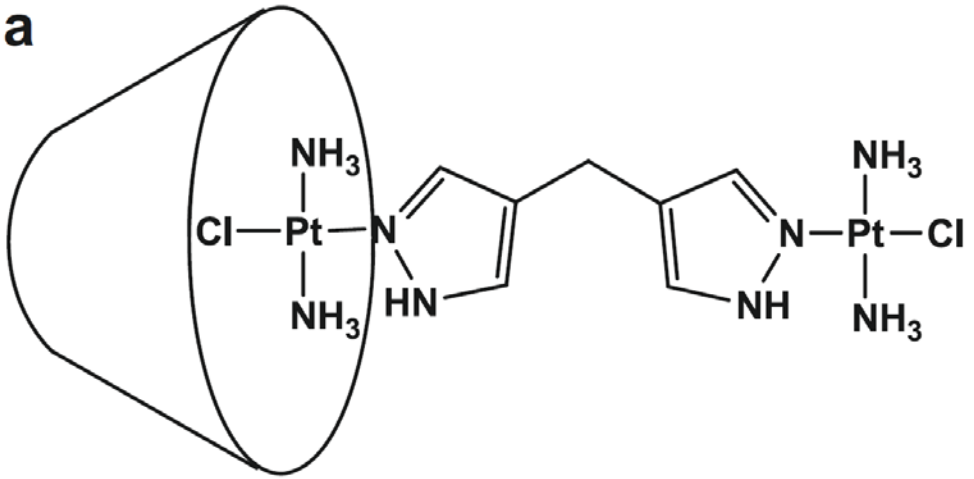
Drug delivery by inclusion in supramolecular macrocycles

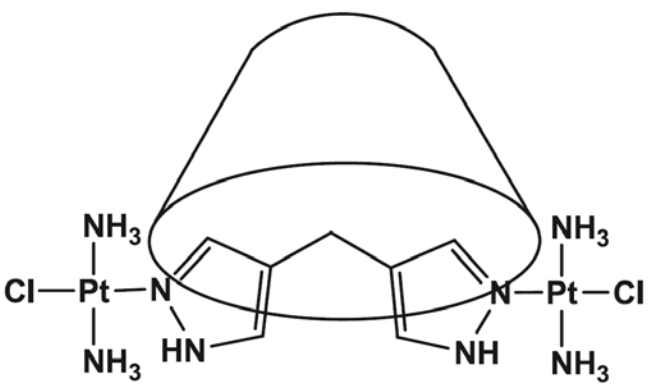
calix[n]arene

Schematic diagrams showing

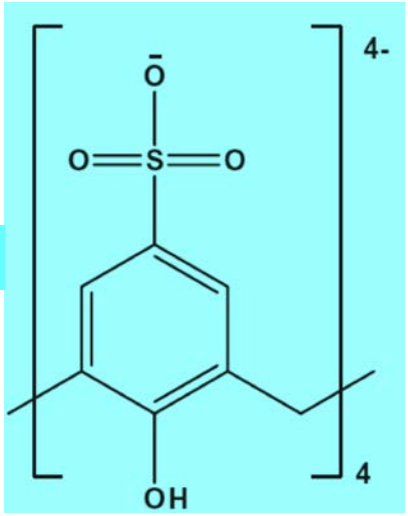
(a) the original proposed end-on binding of s-CX[4] to the platinum group(s) of di-Pt

(b) the actual side-on binding that places the central bridging ligand of di-Pt within the s-CX[4] cavity.





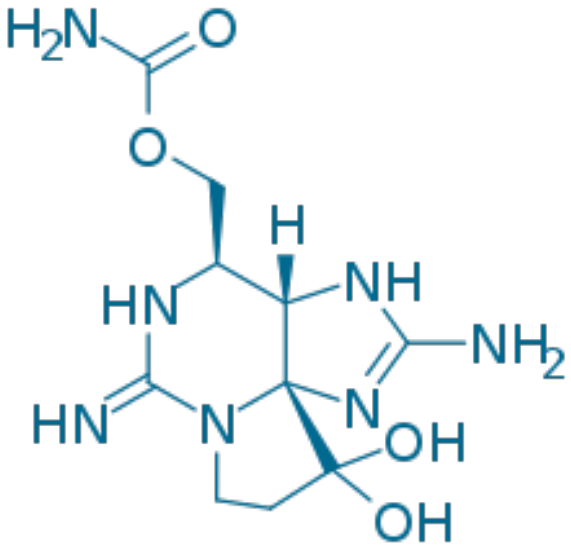
p-sulphonatocalix[4]arene (s-CX[4])

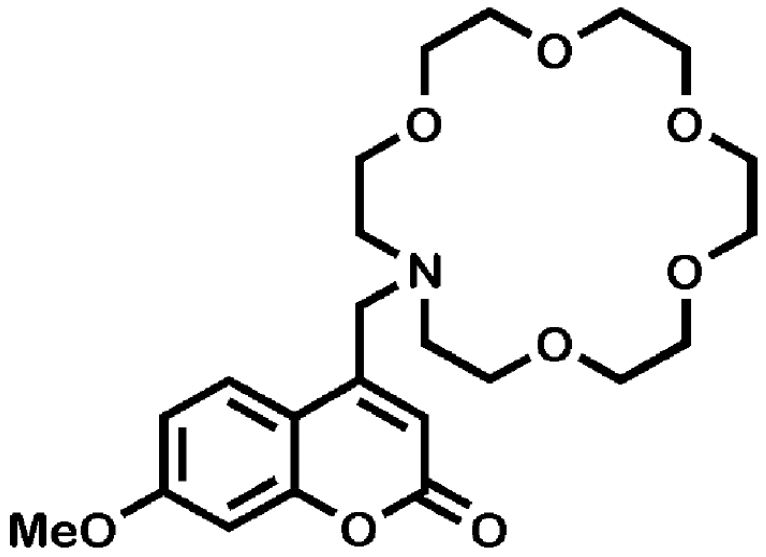


Ref: 8

Crown ethers

Crown ethers, due to their limited size and typical preference for small cations as guest, have not been extensively explored for drug delivery. Yet, the members of the crown ether family can bind and sequester the small molecule *neurotoxin Saxitoxin*, suggesting that for certain drug structures crown ether complexation could be possible.



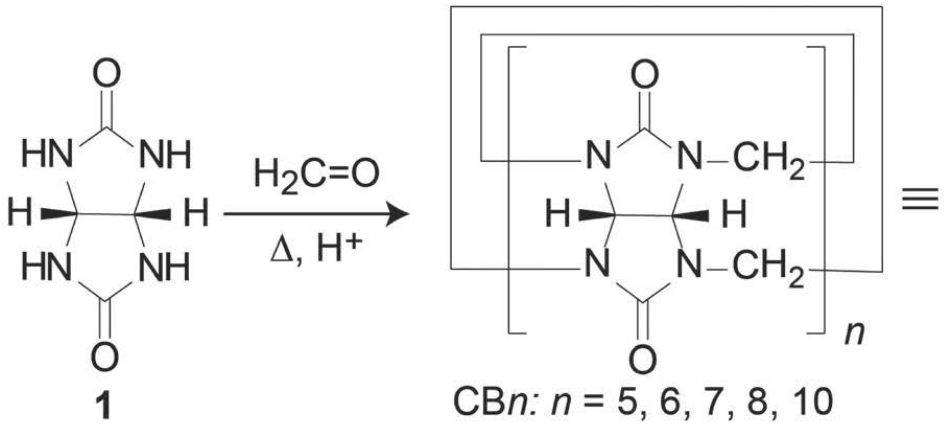


Ref: 9

Drug delivery by inclusion in supramolecular macrocycles

➢ cucurbit[n]uril

These macrocycles are created from acid-catalyzed polymerization of glycouril and formaldehyde to form rigid cyclized host molecules, with the number of glycouril units (n) incorporated into the resulting macrocycle being 5, 6, 7, 8, and 10.



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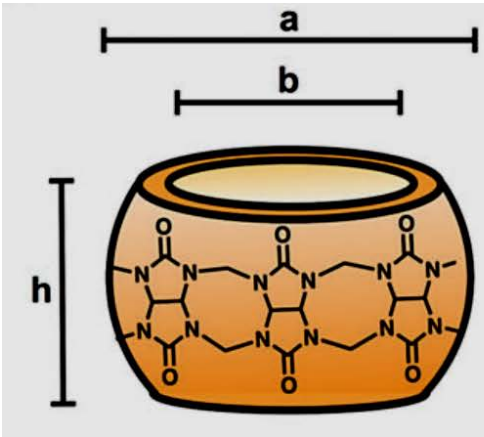


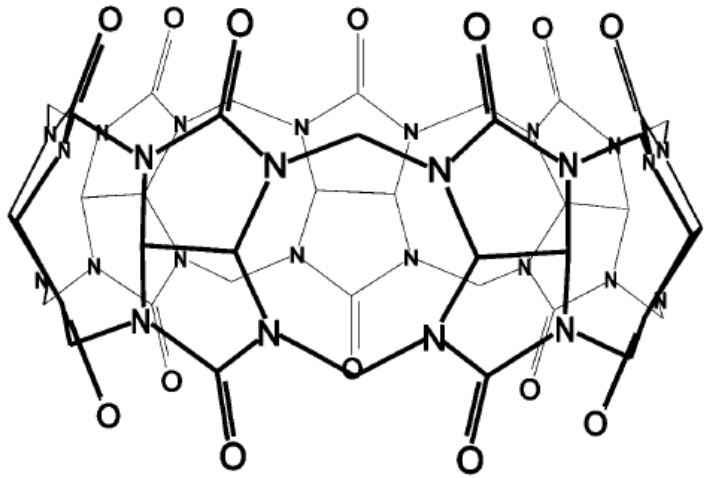
Property	CB[6]	CB[7]	CB[8]
# of gylcouril units	6	7	8
Molecular weight	997	1163	1329
External diameter (a)	14.4 Å	16.0 Å	17.5 Å
Internal diameter (b)	3.9 Å	5.4 Å	6.9 Å
Height (h)	9.1 Å	9.1 Å	9.1 Å
Cavity volume	164 Å^3	279 Å^3	479 Å^3

Ref: 2, 10

Drug delivery by inclusion in supramolecular macrocycles

cucurbit[n]uril

Inclusion within CB[7] can significantly extend stability and activity of drugs in their active form. The chemotherapeutic drug oxaliplatin can be encapsulated in CB[7] which promotes stability of the drug and may also reduce its undesirable side-effects. A broad structural diversity of other small molecule drugs that include *Beta blockers*, *Antidiabetics*, *Enzyme inhibitors*, *Anti-neoplastics*, and *Anesthetics*, which can vary by several hundred dalton in molecular weight, have also been shown to bind to members of the CB[n] family; CB[7] is most commonly used as a result of its relatively high water solubility in comparison to CB[6] or CB[8].



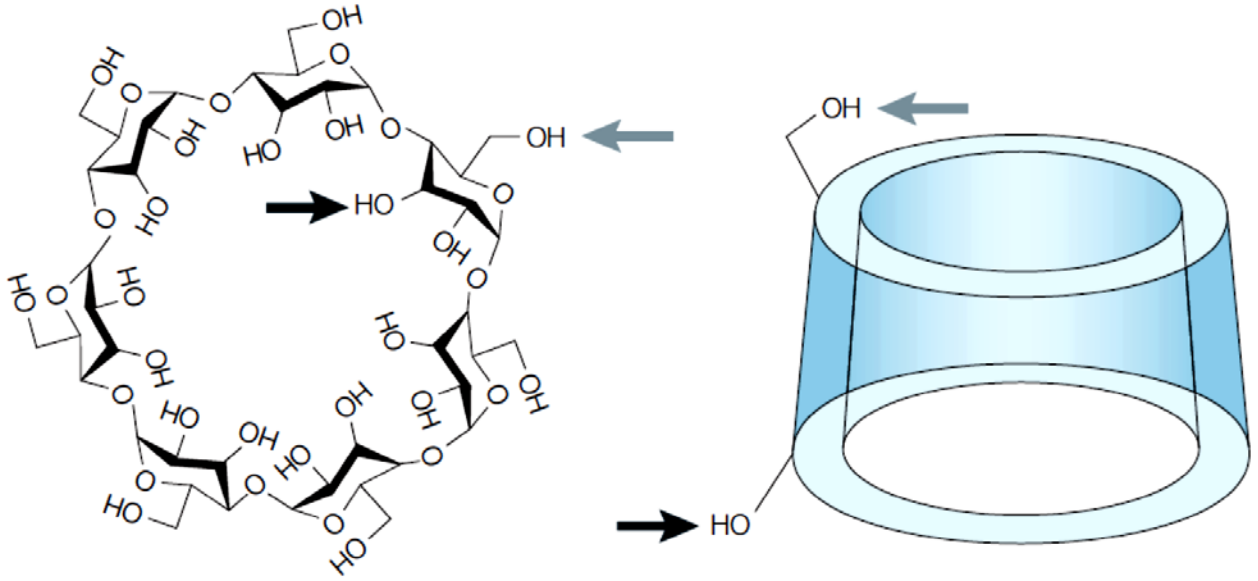
CB7

Ref: 11

Inclusion of drug within cyclodextrin macrocycles

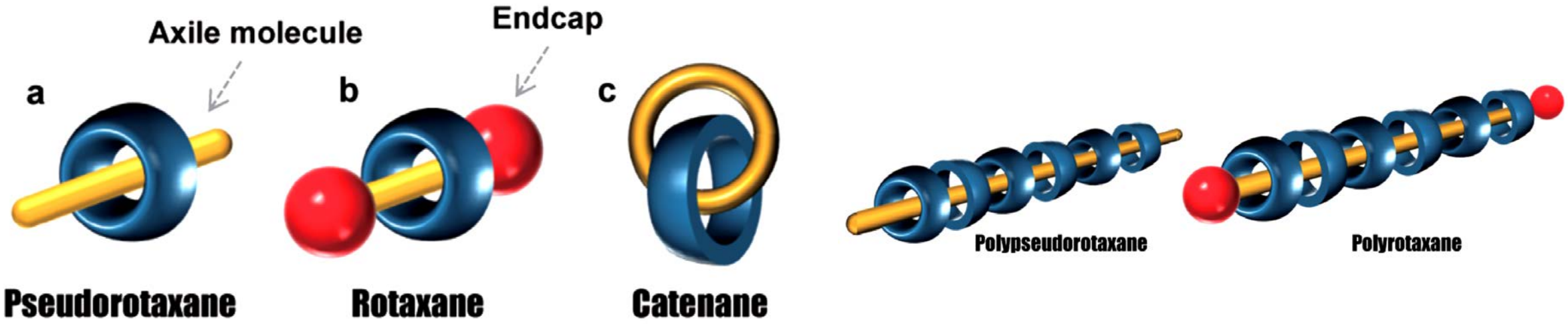
➢ cyclodextrin

The family of cyclodextrin macrocycles is created through cyclic polymerization of glucosemonomers. Using enzymatic conversion of a starch feedstock in bacteria, three primary variants of cyclodextrin are realized that differ in the number of glucose units making up their structure. Cyclodextrins have a long history of contributing to the practice of drug delivery. In 1953, a patent was issued in Germany entitled (translated) "*Method for preparation of inclusion compounds of physiologically active organic compounds*" which described how complexation with different cyclodextrins enhanced the chemical stability of biologically active compounds, increased their duration of action, and improved their taste.



Ref: 2, 12

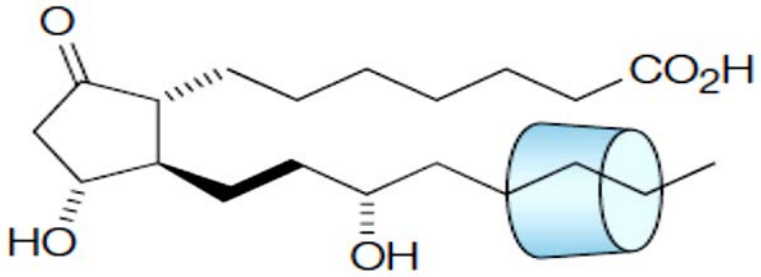
CyDs are safe and inexpensive materials, and therefore a large number of CyD-based supermolecules have been developed. Mechanically interlocked molecules, such as rotaxanes and catenanes, are representative CyD-based supermolecules. Rotaxanes are obtained by threading linear compounds through macrocyclic compounds (pseudorotaxanes; a) and capping their terminals with bulky compounds(b). In contrast, catenanes are obtained by cyclization of pseudorotaxanes(c).



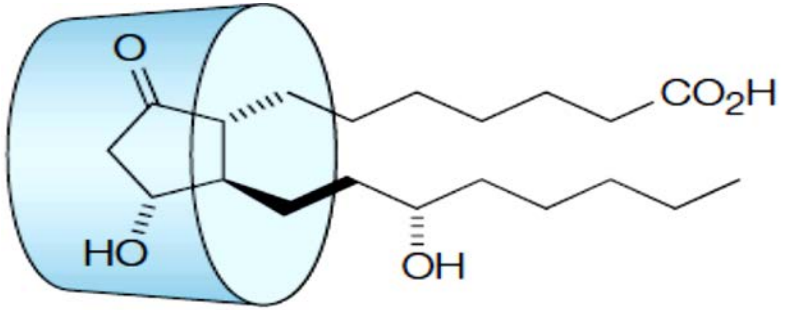
Ref: 1

Proposed models of inclusion complexes between *prostaglandin E2* and (a) α-CD, (b) β-CD and (c) γ-CD

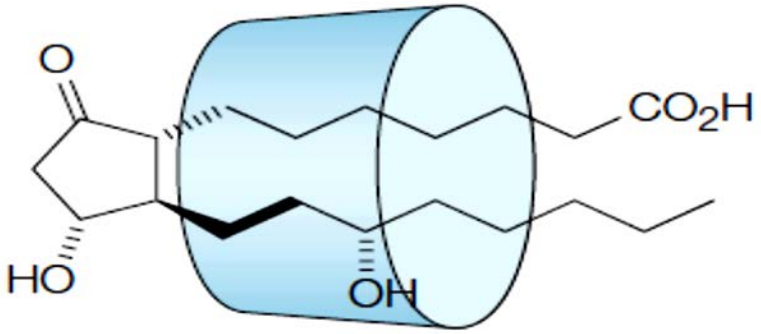
α-CD



β-CD



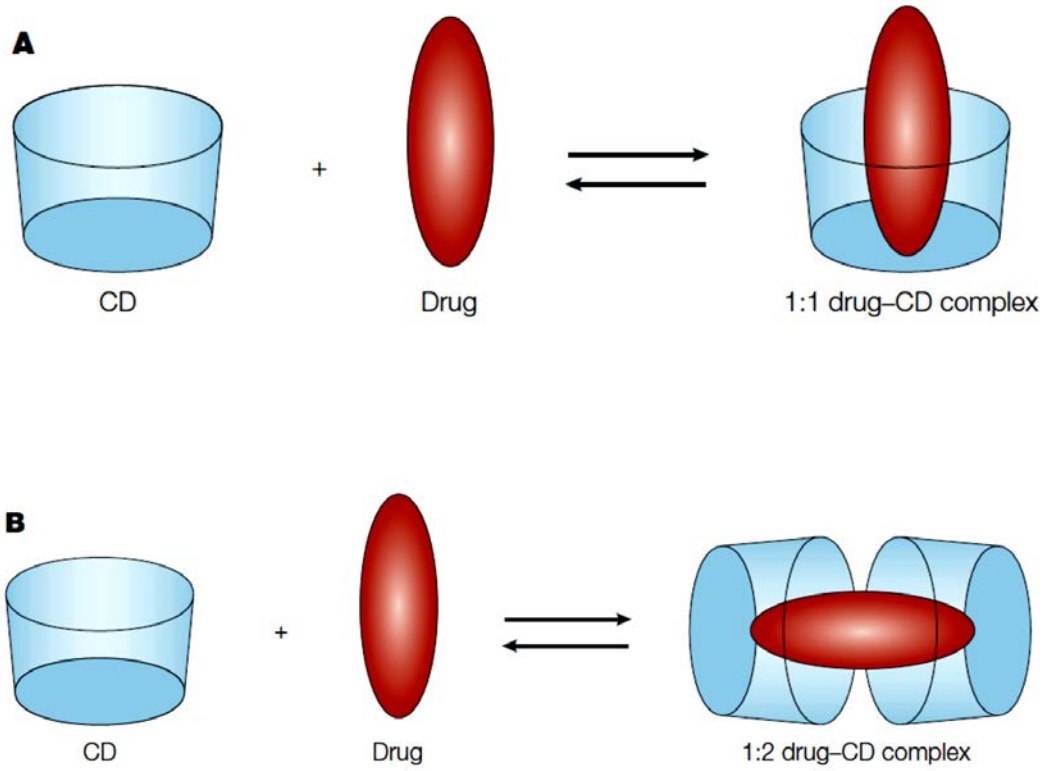
γ-CD



Ref: 12

Cyclodextrins (CDs) can be used to achieve the following:

- **Enhance solubility**
- **Enhance bioavailability**
- **Enhance stability**
- **Convert liquids and oils to free-flowing powders**
- **Reduce evaporation and stabilize flavours**
- **Reduce odours and tastes**
- **Reduce haemolysis**
- **Prevent admixture incompatibilities**



Ref: 2, 12

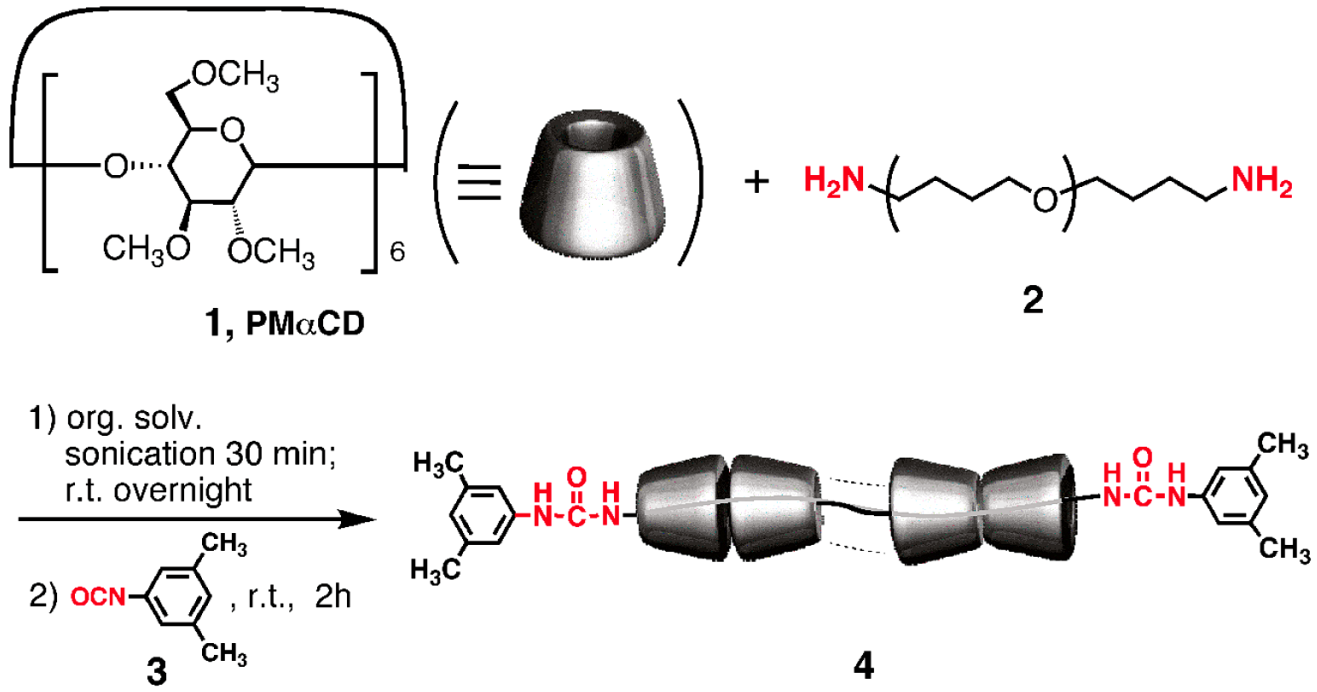
Approved and marketed drug–cyclodextrin* complexes in various world markets

Drug	Administration route	Trade name	Market
α-Cyclodextrin			
Alprostadil (PGE_1)	Intravenous	Prostavastin, Caverject, Edex	Europe, Japan, United States
Cefotiam hexetil HCl	Oral	Pansporin T	Japan
Limaprost	Oral	Opalmon, Prorenal	
β-Cyclodextrin			
Benexate	Oral	Ulgut, Lonmiel	Japan
Dexamethasone	Dermal	Glymesason	Japan
Iodine	Topical	Mena-Gargle	Japan
Nicotine	Sublingual	Nicorette	Europe
Nimesulide	Oral	Nimedex, Mesulid	Europe
Nitroglycerin	Sublingual	Nitropen	Japan
Omeprazole	Oral	Omebeta	Europe
Dinoprostone (PGE_2)	Sublingual	Prostarmon E	Japan
Piroxicam	Oral	Brexin	Europe
Tiaprofenic acid	Oral	Surgamyl	Europe
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Rectal	Propulsid	Europe
Hydrocortisone	Buccal	Dexocort	Europe
Indomethacin	Eye drops	Indocid	Europe
Itraconazole	Oral, intravenous	Sporanox	Europe, United States
Mitomycin	Intravenous	Mitozytrex	United States

Ref: 12

To design CyD polyrotaxane-based biomaterials and drug carriers, chemical modification of CyD in the polyrotaxanes is often required because CyD polyrotaxanes are generally poorly water-soluble in water. However, to yield CyD polyrotaxane derivatives, multi-step synthesis pathways are often needed.

Takata and colleagues reported one-pot synthesis of polyrotaxanes with 2,3,6-tri-O-methyl α-CyD (TM-α-CyD).



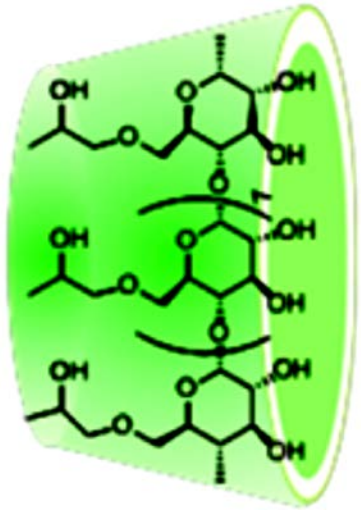
Ref: 1, 13

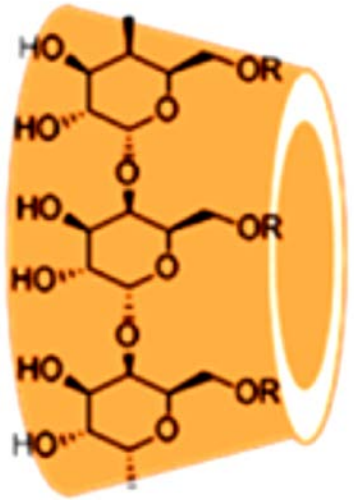
Thompson and colleagues prepared hydroxypropylated polyrotaxanes through ***Takata's*** method. 2-Hydroxypropyl *β*-CyD (HP-*β*-CyD) was directly used to yield polyrotaxanes, and the reaction was performed in organic solvents such as hexane. His group also prepared various water-soluble polyrotaxanes including HP-*β*-CyD and 4-sulfobutyl ether *β*-CyD (SBE-*β*-CyD) using the same method.

HP-β-CD

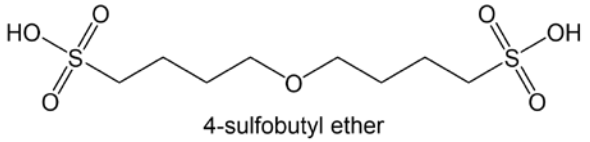
Me-β-CD =

azido-β-CD

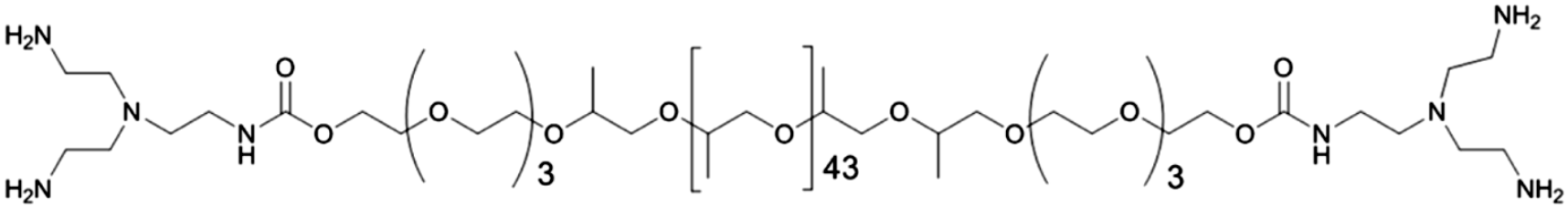




= **SBE-β-CD**



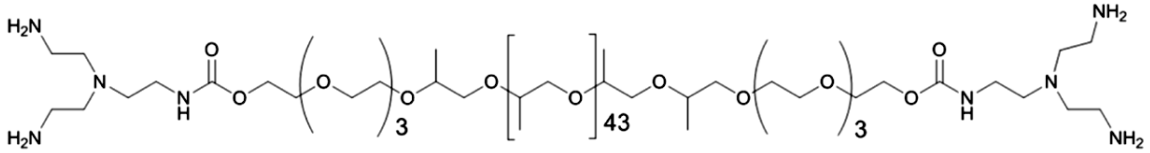
4-sulfobutyl ether

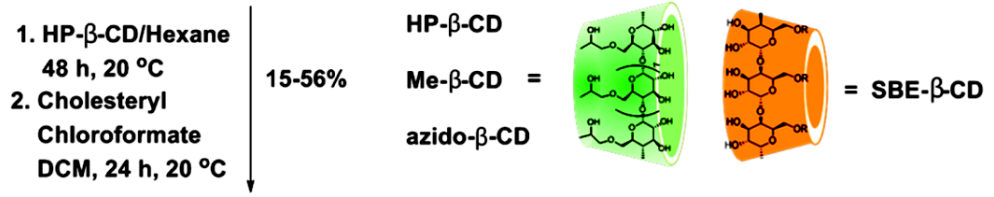


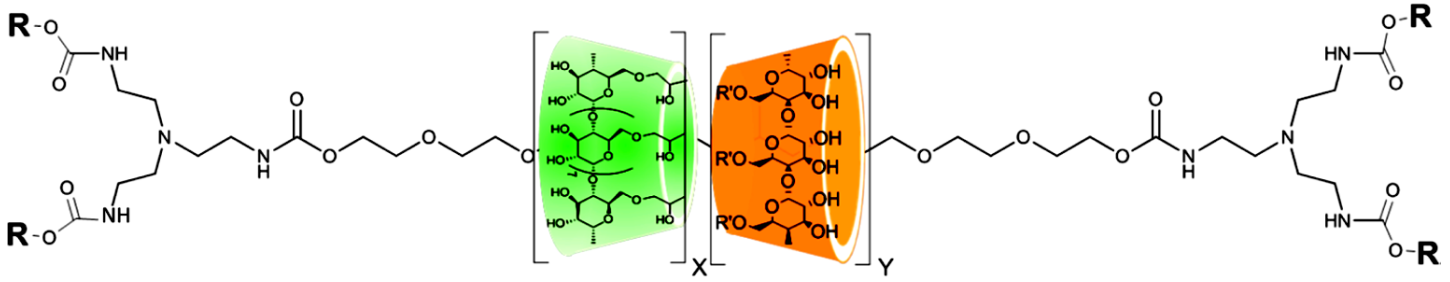
Ref: 14

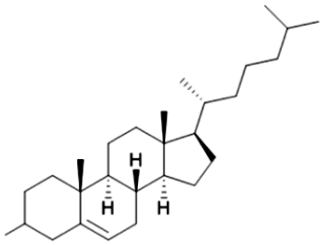
Cyclodextrin-Based Supramolecular Chemistry for Pharmaceutical Sciences

Synthesis Pathway Employed for β-CD/SBE-β-CD Mixed PR Derivatives

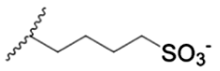








R = Cholesterol

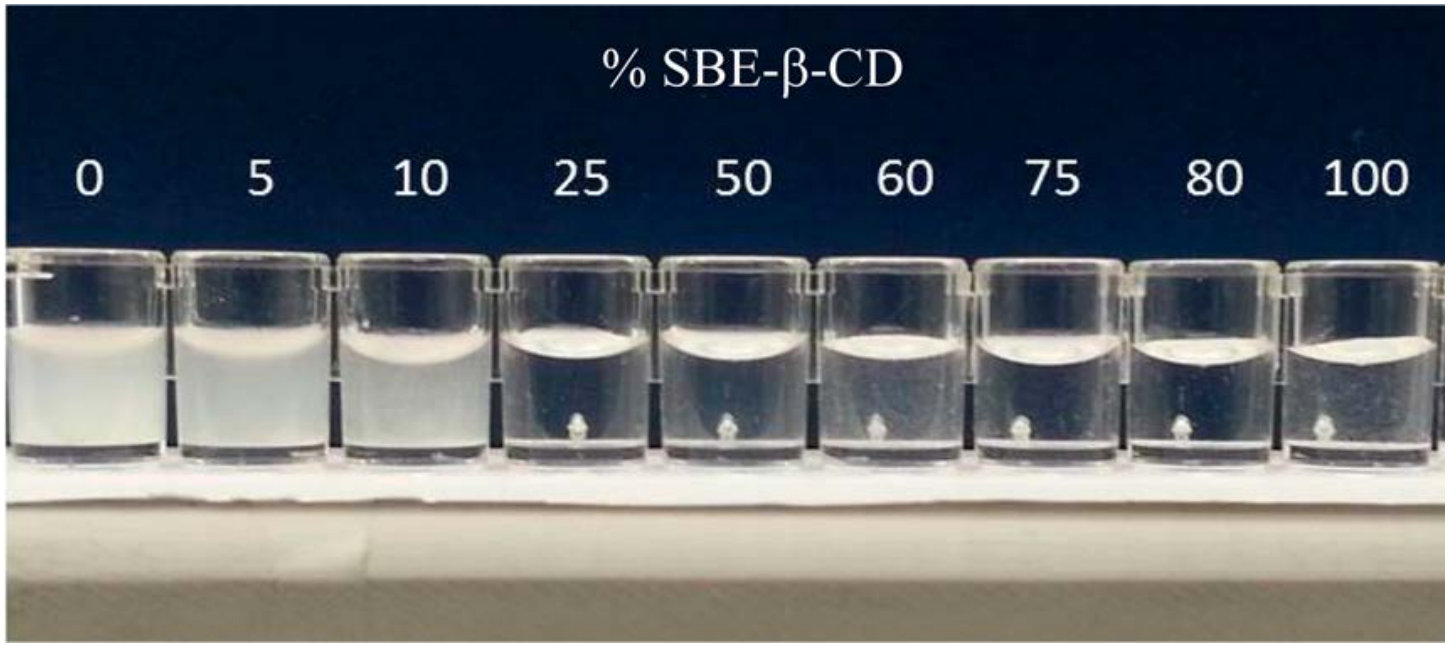


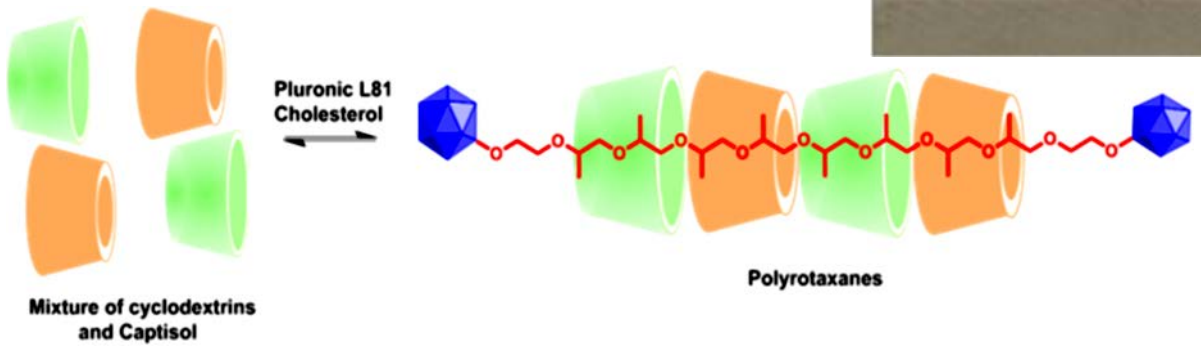
R' = Sulfobutyl

Ref: 14

Polyrotaxanes containing mixtures of HP-β-CD and SBE-β-CD were screened and found to be biologically active in an in vitro model of *Niemann-Pick Type C disease* where they mobilize aberrantly stored cholesterol similarly to monomeric cyclodextrin controls.

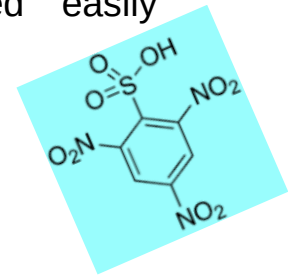
Water solubility of the HP-β-CD/SBE -βCD/Pluronic L81 PRs at 50 mg/mL.

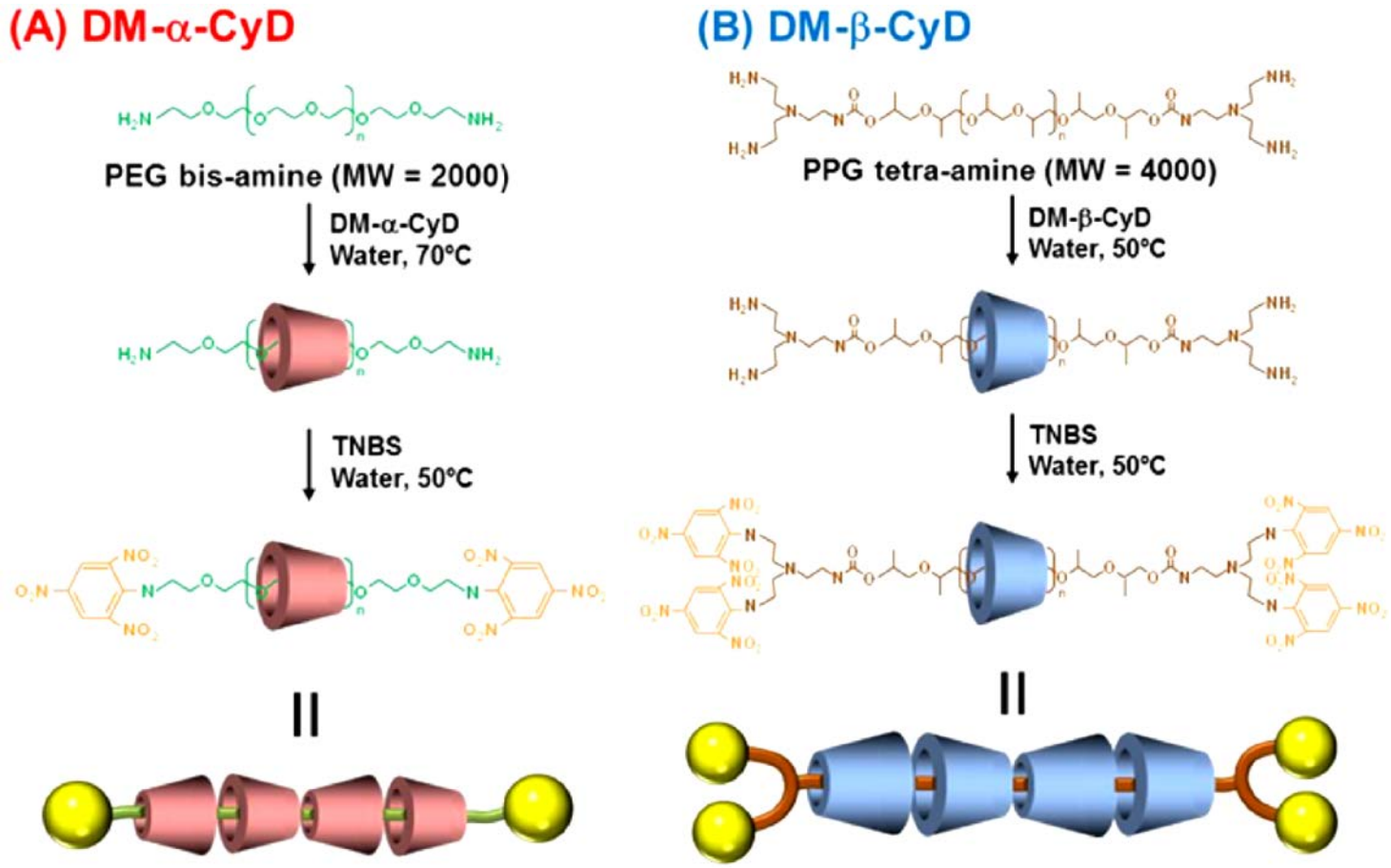




Ref: 14

recently demonstrated a novel strategy for the efficient preparation of polypseudorotaxanes and polyrotaxanes with 2,6-di-*O*-methyl *α*-CyD (DM-*α*-CyD) and DM-*β*-CyD by using the cloud points of DM-CyDs. Both DM-*α*-CyD and DM-*β*-CyD easily formed polypseudorotaxanes in water at high temperature. Subsequently, polyrotaxanes were obtained by adding 2,4,6-trinitrobenzenesulfonic acid (TNBS) as an end-cap, resulting in the one-pot synthesis of DM-CyD polyrotaxanes in water. These methods are very useful because polyrotaxane derivatives are prepared easily without organic solvents.



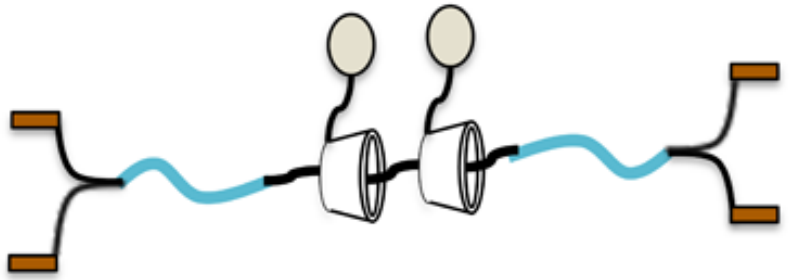


Ref: 15

Pharmacokinetics of Cyclodextrin-Based Supermolecules

Interlocked molecules such as polyrotaxanes and polycatenanes can maintain their structure in the body after parenteral administration.

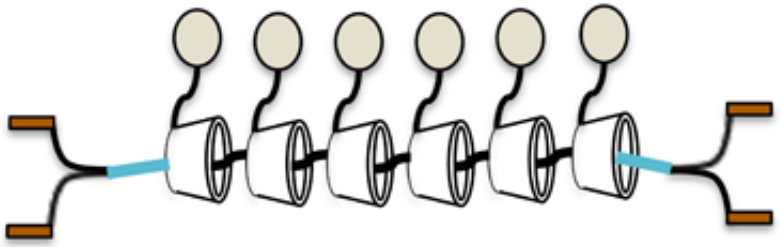
Collins et al. demonstrated that the lowly threaded HP-β-CyD polyrotaxanes show rapid clearance and accumulation in the lung. In contrast, highly threaded HP-β-CyD polyrotaxanes exhibit prolonged circulation in blood and high accumulation in the liver. These polyrotaxanes mainly adsorb lipoproteins because of the presence of cholesterol moieties as end-caps.



Low Threading Polyrotaxane

Rapid Blood Clearance

Increased Lung Deposition



High Threading Polyrotaxane

Extended Blood Circulation

Increased Liver Deposition

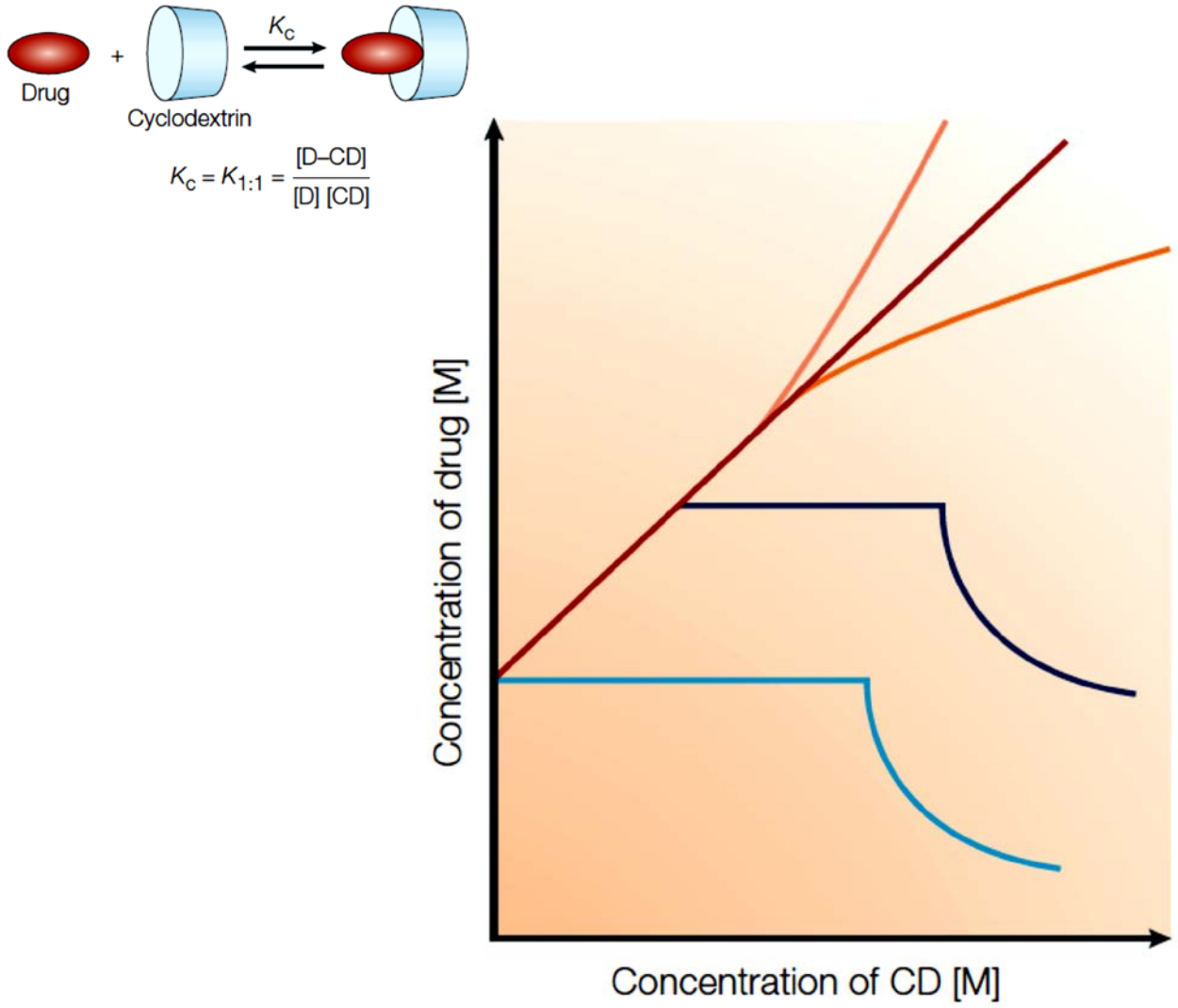
Ref: 16

Pharmacokinetics of Cyclodextrin-Based Supermolecules

Solubilization with cyclodextrins:

Cyclodextrins (CDs) can enhance apparent water solubility by forming dynamic,non-covalent, water-soluble inclusion complexes as depicted in the figure. This interaction is an equilibrium governed by an equilibrium constant,*K*c.

The nature of the complex, as well as the numerical value of the equilibrium constant, can be derived from from measuring a particular property of the complex as a function of drug and CD concentrations. In phase-solubility analysis, the increased solubility is assessed as a function of CD concentration. As illustrated, a number of solubility profiles are possible, each giving insight into the type of complex formed, as well as its stoichiometry. An A-type\ profile (red line) represents the formation of soluble CD complexes, whereas B-type systems (blue line) indicate the formation of complexes of limited solubility.

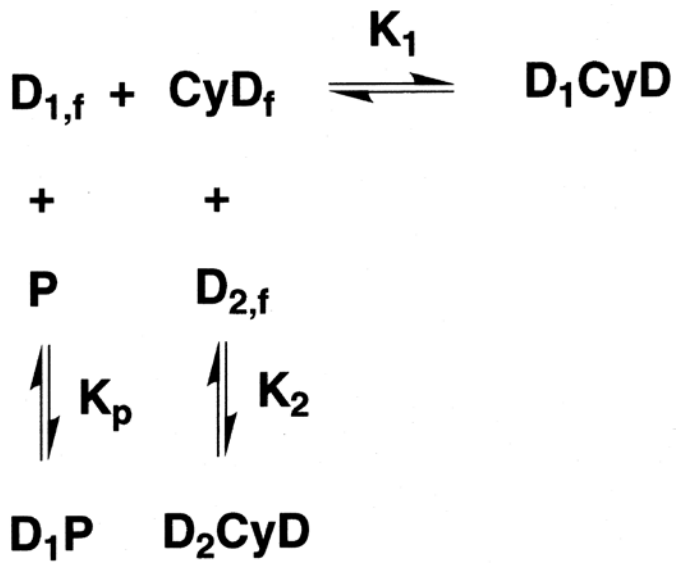


Ref: 12

Pharmacokinetics of Cyclodextrin-Based Supermolecules

Stella reported that in parenteral administration, the major driving force for dissociation of weakly or moderately interacting guest molecules with CyDs is simple dilution.

Drug binding to plasma and tissue proteins is a complex phenomenon and generally involves multiple equilibria. Therefore, only this simplified model of protein binding will be considered here. These equations along with the component mass balance equations can be solved to determine the free fraction of drug to cyclodextrin as a function of the extent of dilution, placing realistic values for the binding constants (K_1,K_2,K_{app}), concentrations of drug, competing agent, cyclodextrin and protein. It is evident that the free fraction of drug will depend on the concentrations of all species involved, the strengths of binding and extent of dilution. It is impossible to illustrate the effects of the entire range of these parameters on the drug release from drug/cyclodextrin complexes.



$$K_1 = [D_1CyD]/([D_{1,f}][CyD_f]$$

$$K_2 = [D_2CyD]/([D_{2,f}][CyD_f]$$

$$K_p = [D_1P]/([D_{1,f}][P]) \Rightarrow K_{app} = [D_1P]/[D_{1,f}]$$

Ref: 17

Pharmacokinetics of Cyclodextrin-Based Supermolecules

To fabricate CyD-based supramolecular carriers, the Kc value between CyDs and guest molecules should be $>10^4$–10^5 M^{-1}. If Kc is $<10^4$ M^{-1}, other parameters such as protein binding of guest molecules, competitive interaction of CyDs with endogenous compounds, and elimination of CyDs should be reduced. Multivalent interaction between some CyD molecules and some guest molecules may also be useful in preventing the dissociation of the complex. Meanwhile, we should note that to form an inclusion complex in the blood with separately administered drugs, CyDs should show higher Kc ($>10^6$–10^7 M^{-1})

Calculation of Drug Fraction Bound to Cyclodextrin in Pure Water ($f_{CD\ pure\ water}$) and in Plasma ($f_{CD\ plasma}$) at HPβCD Concentration of 106 μg/mL (Corresponding to 0.106 g/L or 7.57×10^{-5} M).

Drug	V_d (L/kg)	MW (Da)	C_{max} (M)	$K_{1:1}$ (M^{-1})	Ref.	$f_{CD\ pure\ water}$ (%)	f_P (%)	$f_{CD\ plasma}$ (%)
Tadalafil	0.9	389	1.3×10^{-6}	360	60	2.7	94	0.2
Telmisartan	7	515	2.8×10^{-6}	40,000	61	75	99	2.9
Testosterone	122	288	6.8×10^{-10}	12,000	62	48	98	1.8
Zolpidem	0.54	307	4.4×10^{-7}	150	63	1.1	93	0.08
Hypothetical drug X	1	–	1.0×10^{-6}	100,000	–	90	99	8.0

V_d, volume of distribution; MW, molecular weight; C_{max}, maximum drug concentration in plasma based on the drug's pharmacokinetics and administration of a normal drug dose[54–56]; $K_{1:1}$, stability constant of 1:1 inclusion complex (with superscripted reference number); $f_{CD\ pure\ water}$, drug fraction bound to cyclodextrin in pure water; f_P, drug fraction bound to protein; $f_{CD\ plasma}$, drug fraction bound to cyclodextrin in plasma.

Ref: 18

Pharmacokinetics of Cyclodextrin-Based Supermolecules

Kurkov *et al.* investigated the effects of CyDs on drug pharmacokinetics after parenteral administration. In the case of *Telmisartan* (Kc=4×10^4 M^{-1}), only 2.9% of the drug bound to HP-β-CyD in plasma, indicating that CyD complexes easily dissociate in plasma. However, *Telmisartan* strongly binds to plasma proteins (>99%). Meanwhile, 7.5% of *Betamethasone* (Kc=3×10^3 M^{-1}) and 3.8% of *Acyclovir* (Kc=8×10^2 M^{-1}) bound to CyDs in plasma; however, their Kc values were smaller than that of telmisartan. *Betamethasone* and *Acyclovir* bound to plasma proteins weakly (64, 33%, respectively).

Calculation of Drug Fraction Bound to Cyclodextrin in Pure Water ($f_{CD\ pure\ water}$) and in Plasma ($f_{CD\ plasma}$) at HPβCD Concentration of 106 μg/mL (Corresponding to 0.106 g/L or 7.57 × 10^{-5} M).

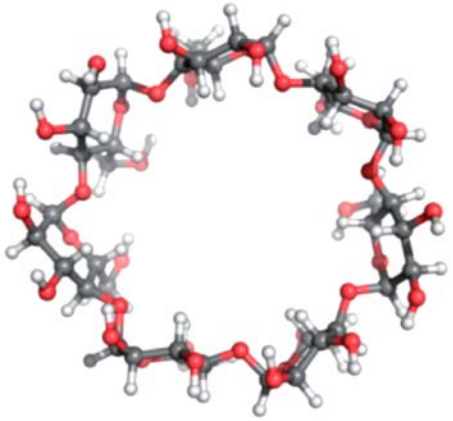
Drug	V_d (L/kg)	MW (Da)	C_{max} (M)	$K_{1:1}$ (M^{-1})	Ref.	$f_{CD\ pure\ water}$ (%)	f_P (%)	$f_{CD\ plasma}$ (%)
Acetaminophen	0.95	151	5.0 × 10^{-5}	400	*a*	3.0	20	0.6
Aspirin	0.15	180	5.3 × 10^{-4}	100	17	0.8	80	0.2
Acetazolamide	0.2	222	1.6 × 10^{-4}	60	*a*	0.5	95	0.02
Acyclovir	0.70	225	7.2 × 10^{-6}	770	18	5.5	33	3.8
Amoxicillin	0.3	365	6.5 × 10^{-5}	2.5	*a*	0.02	20	0.02
Atropine	2.0	289	7.4 × 10^{-9}	65	*a*	0.49	50	0.00
Betamethasone	1.2	393	2.9 × 10^{-7}	3000	19	18	64	7.5
Bimatoprost	0.67	416	1.9 × 10^{-10}	1900	*b*	13	88	1.7
Budesonide	3.0	431	5.4 × 10^{-6}	3300	20	20	90	2.4
Bupivacaine	1.0	288	6.9 × 10^{-6}	13	21	0.1	95	0.00
Ibuprofen	0.18	206	2.8 × 10^{-4}	5000	47	27	99	0.4
Indomethacin	1	358	5.6 × 10^{-6}	700	48	5.0	99	0.05
Ketoprofen	0.15	254	1.9 × 10^{-5}	11	*a*	0.8	99	0.001
Ketorolac	0.21	376	1.8 × 10^{-6}	27	*a*	2.0	99	0.02
Lidocaine	1.1	234	5.6 × 10^{-6}	17	*a*	0.13	70	0.04

Ref: 18

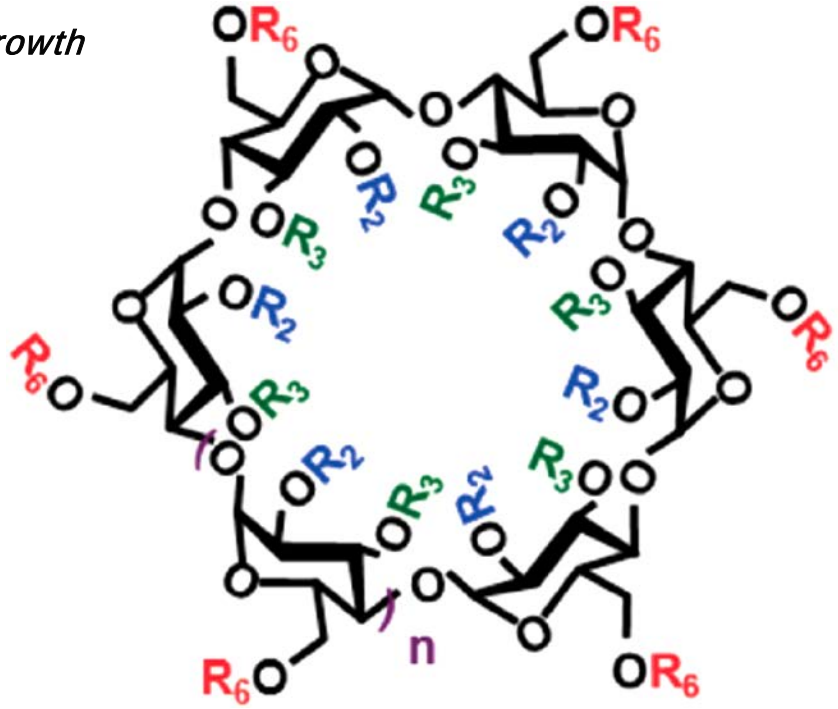
Cyclodextrin-Based Supramolecular Pharmacology and Drug Discovery

Recently, various bioactivities of CyDs have been demonstrated, and CyDs have been used as ***active pharmaceutical ingredients (APIs)*** against:

Niemann–Pick disease type C (NPC), leukemia, hyperlipidemia, Alzheimer's disease cerebral ischemic injury, atherosclerosis, diabetic kidney disease, chronic renal failure AIDS, influenza, peripheral artery disease, sterility, solid cancers, bacterial growth α-synucleinopathy, GM1- gangliosidosis, septic shock, hypervitaminosis transthyretin-related familial amyloidotic polyneuropathy (FAP).



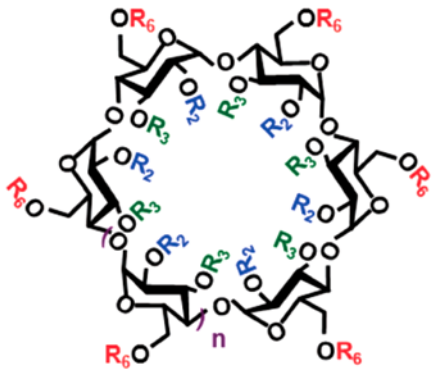
Glucose unit
6 : α-CyDs
7 : β-CyDs
8 : γ-CyDs



Ref: 1

Cyclodextrin-Based Supramolecular Pharmacology and Drug Discovery

Examples of CyD Derivatives Used asactive pharmaceutical ingredients(APIs)



CyD	Substitution (R)	Disease (symptom)	Property
Sugammadex	R_2: H R_3: H R_6: Carboxyl thio ether	·Neuromuscular blockade by rocuronium	Interacts with rocuronium in the blood and accelerates its elimination
HP-β-CyD	R_2: H or $CH_2CH(OH)CH_3$ R_3: H or $CH_2CH(OH)CH_3$ R_6: H or $CH_2CH(OH)CH_3$	·NPC ·Leukemia ·Hyperlipidemia ·Alzheimer's disease ·Adjuvant ·Cerebral ischemic injury ·Atherosclerosis ·Diabetic kidney disease ·Chronic renal failure	Interacts with cholesterol, phospholipids, proteins and uremic toxins in the blood, on the cells, in the cells and in the gastrointestinal tract
	R_2: H or $CH_2CH(OH)CH_3$ R_3: H or $CH_2CH(OH)CH_3$ R_6: H or $CH_2CH(OH)CH_3$	·NPC	Interacts with biological membranes and affects the cell function
R8-β-CyD	R_2: H R_3: H R_6: H or octaarginine	·NPC	Aggressively enters the cells, and interacts with biological membranes
Lac-β-CyD	R_2: H R_3: H R_6: H or lactose	·NPC (hepatosplenomegaly)	Aggressively enters the hepatic parenchymal cells, and interacts with biological membranes

Ref: 1

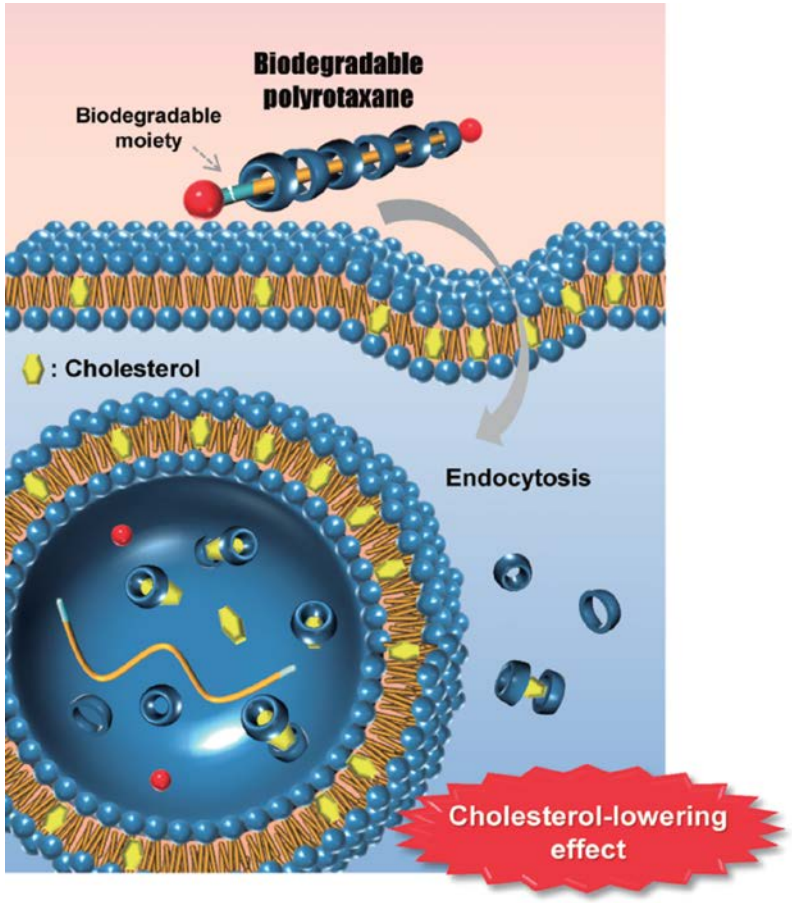
Cyclodextrin-Based Supramolecular Pharmacology and Drug Discovery

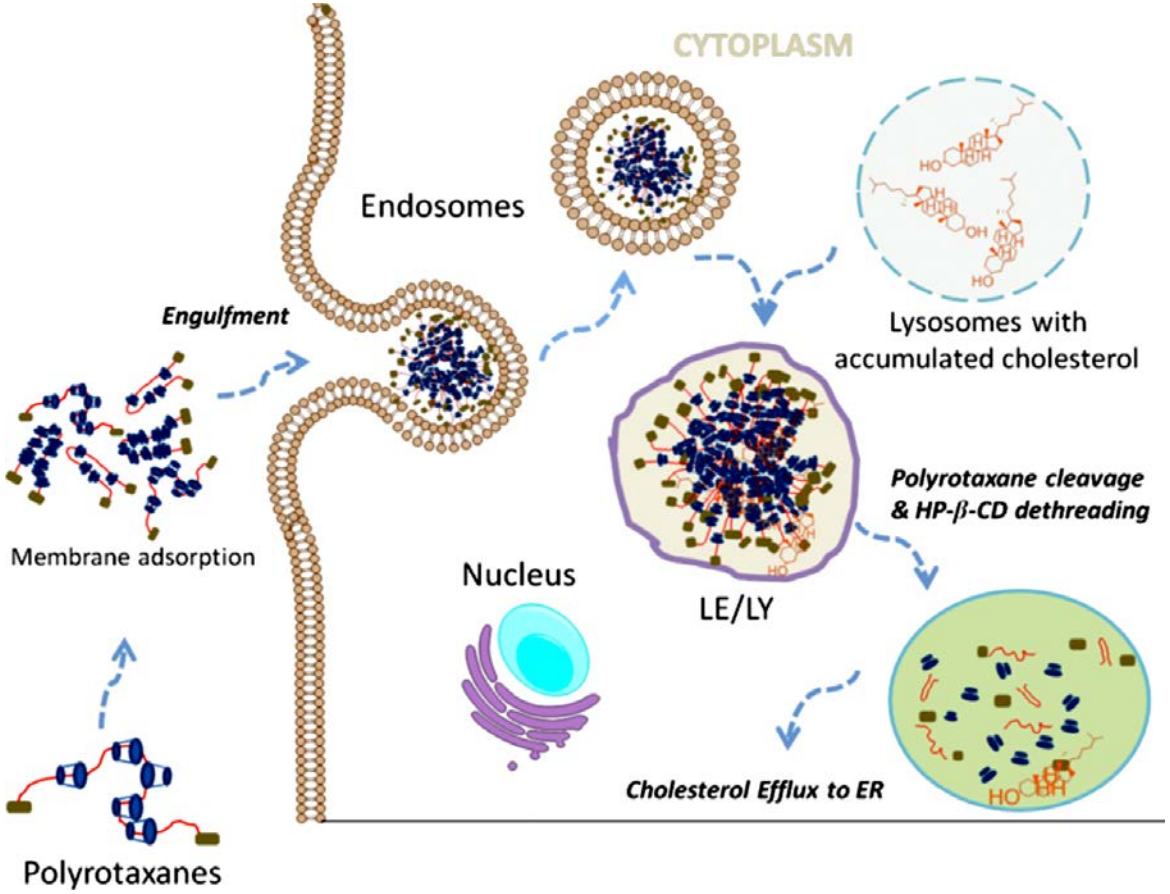
Examples of CyD Derivatives Used asactive pharmaceutical ingredients(APIs)

S-CyDs	R_2: H R_3: H R_6: SO_3H	·AIDS	Inhibition of the binding of HIV virions to the cells
Pentacyclic triterpene-M-β-CyD	R_2: CH_3 R_3: CH_3 R_6: SO_3H	·AIDS ·Influenza	Inhibition of the binding of virions to the cells
M-β-CyD	R_2: H or CH_3 R_3: H or CH_3 R_6: H or CH_3	·NPC ·Sterility ·Solid cancer ·Bacterial growth ·α-Synucleinopathy	Interacts with biological membranes and affects the cell or sperm function
DM-α-CyD	R_2: CH_3 R_3: H R_6: CH_3	·GM1-gangliosidosis ·Septic shock	Interacts with biological membranes and affects the cell function
DM-β-CyD	R_2: CH_3 R_3: H R_6: CH_3	·Hypervitaminosis	Interacts with vitamin A in the blood and accelerates its elimination
FA-M-β-CyD	R_2: H or CH_3 R_3: H or CH_3 R_6: H or CH_3 or folate	·Solid cancer	Cancer cell-selective antitumor activity mediated by the regulation of mitophagy
DMA-β-CyD	R_2: H or CH_3 R_3: H or $COCH_3$ R_6: H or CH_3	·Septic shock	Directly interacts with lipopolysaccharide
GUG-β-CyD	R_2: H R_3: H R_6: H or glucuronylglucose	·FAP	Inhibits the formation of the amyloid

Ref: 1

Proposed Mechanism for the Cholesterol-Lowering Effect of Biodegradable Polyrotaxanes

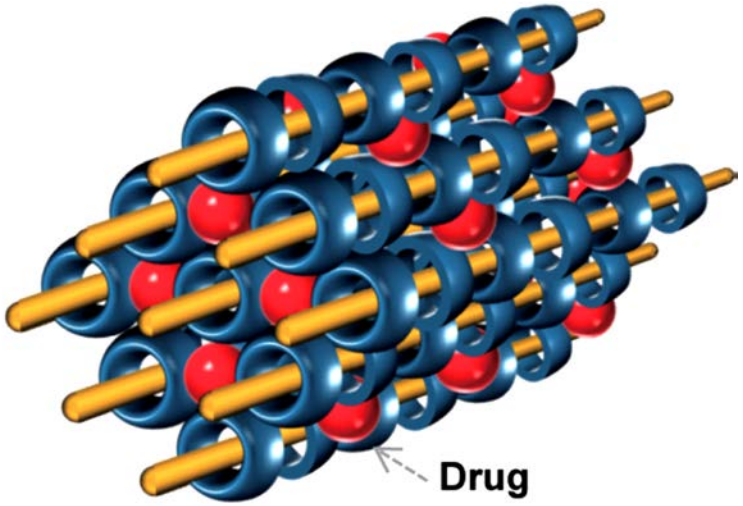




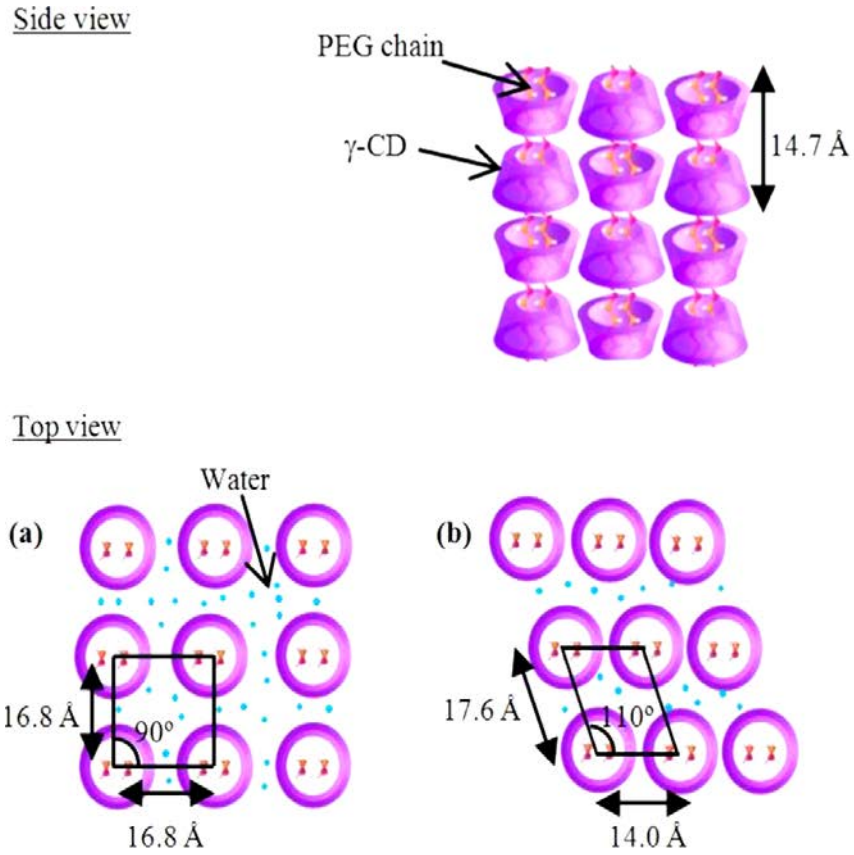
Ref: 1, 19

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

Higashi et al. investigated the usefulness of PEG/CyD polypseudorotaxanesas pharmaceutical materials for hydrophilic drugs such as ***salicylic acid, salicylamide, piroxicam, and hydrocortisone***.



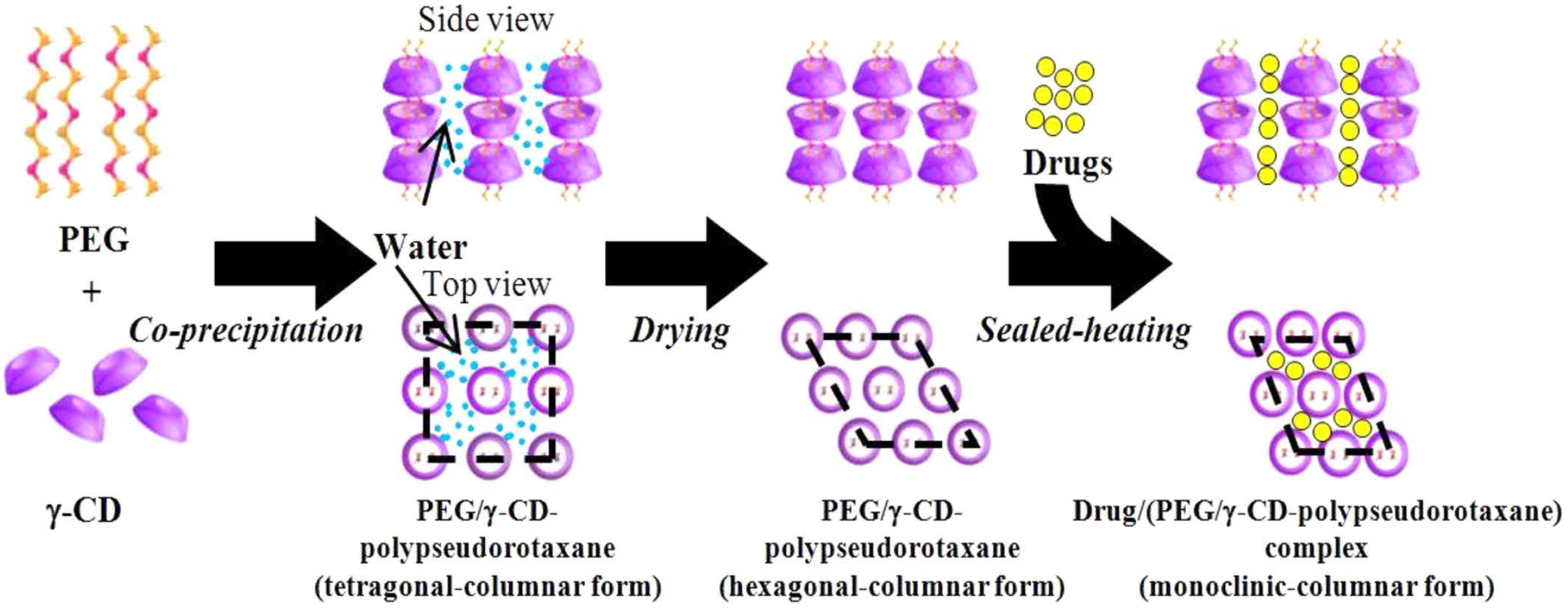
Polypseudorotaxane/drug solid dispersion



tetragonal-columnar form monoclinic-columnar form hexagonal-columnar form.

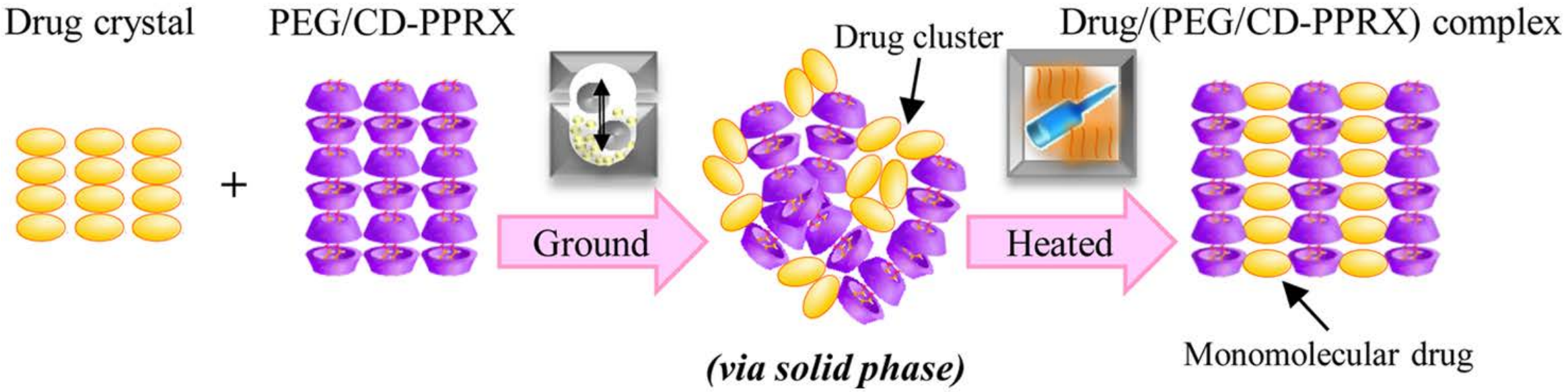
Ref: 1, 20

Cyclodextrin-Based Supramolecular Physical Pharmaceutics



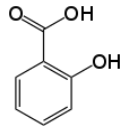
Ref: 20

Cyclodextrin-Based Supramolecular Physical Pharmaceutics



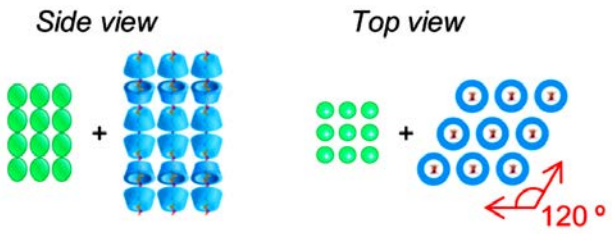
Ref: 21

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

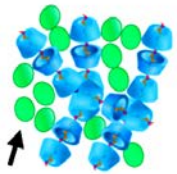


Salicylic acid

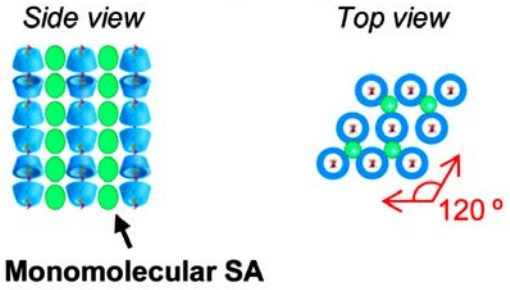
PM: PXRD pattern (c)
SA (crystal) +PEG/α-CD-PPRX (HC form of α-CD)

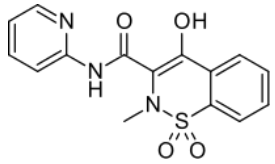


GM: PXRD pattern (e)
Amorphous mixture of SA and PEG/α-CD-PPRX



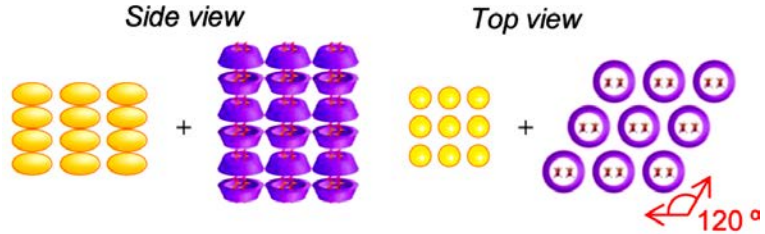
Heated-GM: PXRD pattern (g)
SA/(PEG/α-CD-PPRX) complex (HC form of α-CD)



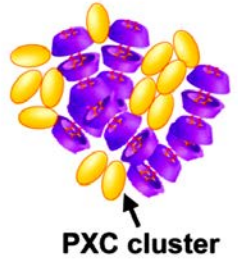


piroxicam

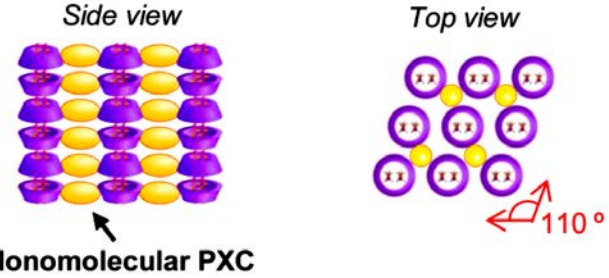
PM: PXRD pattern (c)
PXC (crystal) +PEG/γ-CD-PPRX (HC form of γ-CD)



GM: PXRD pattern (d)
Amorphous mixture of PXC and PEG/γ-CD-PPRX

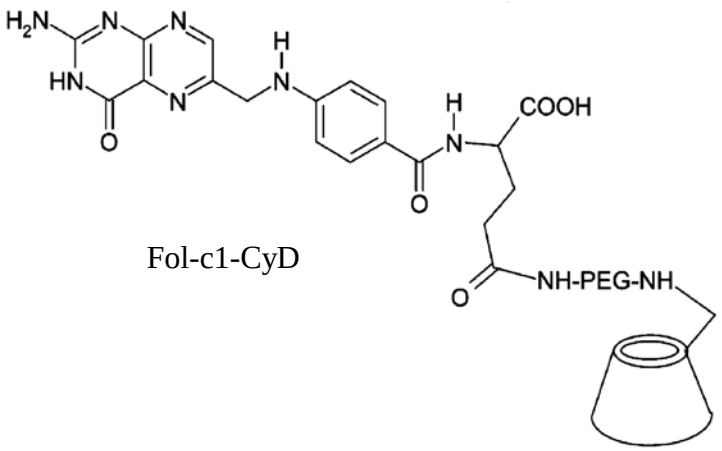


Heated-GM: PXRD pattern (f)
PXC/(PEG/γ-CD-PPRX) complex (MC form of γ-CD)

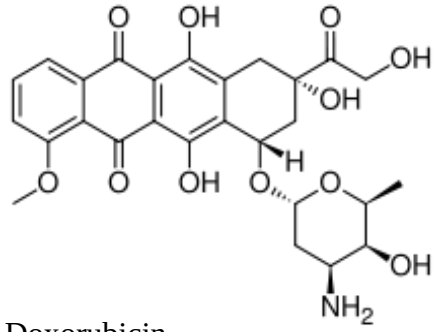


Ref: 21

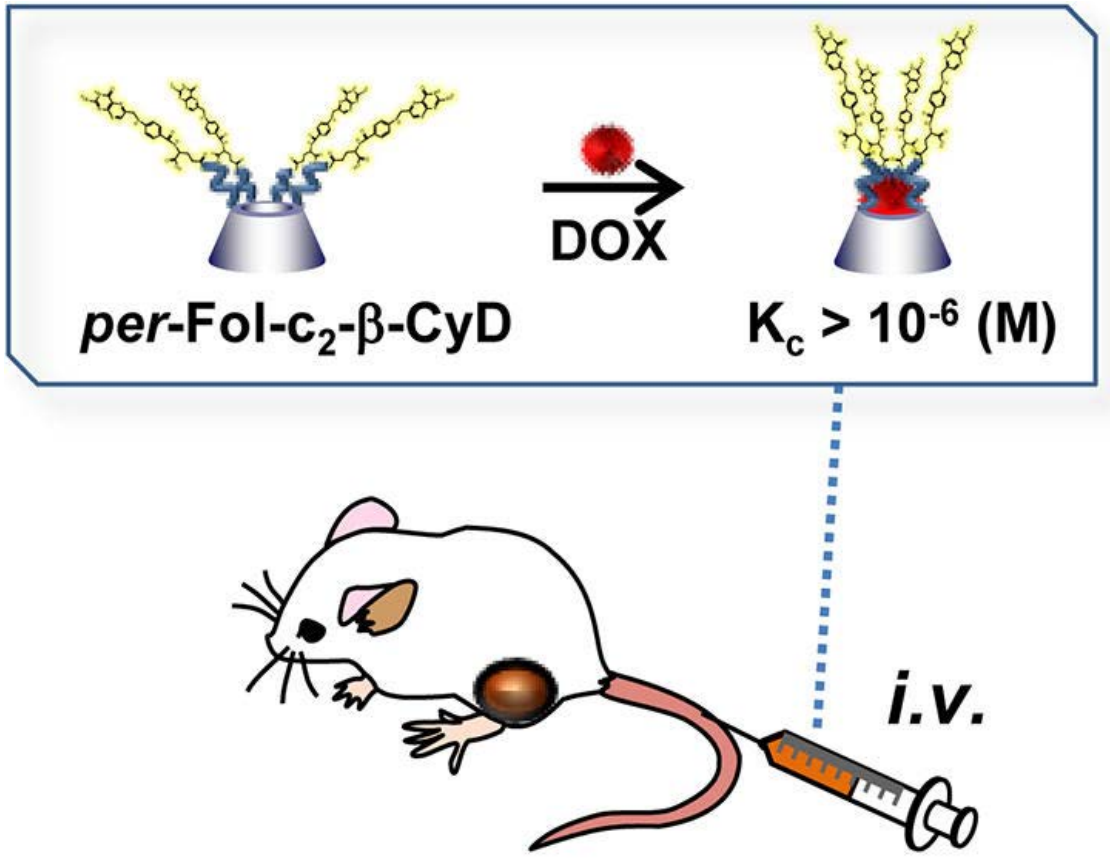
Cyclodextrin-Based Supramolecular Physical Pharmaceutics



Fol-c1-CyD



Doxorubicin
trade names **Adriamycin**

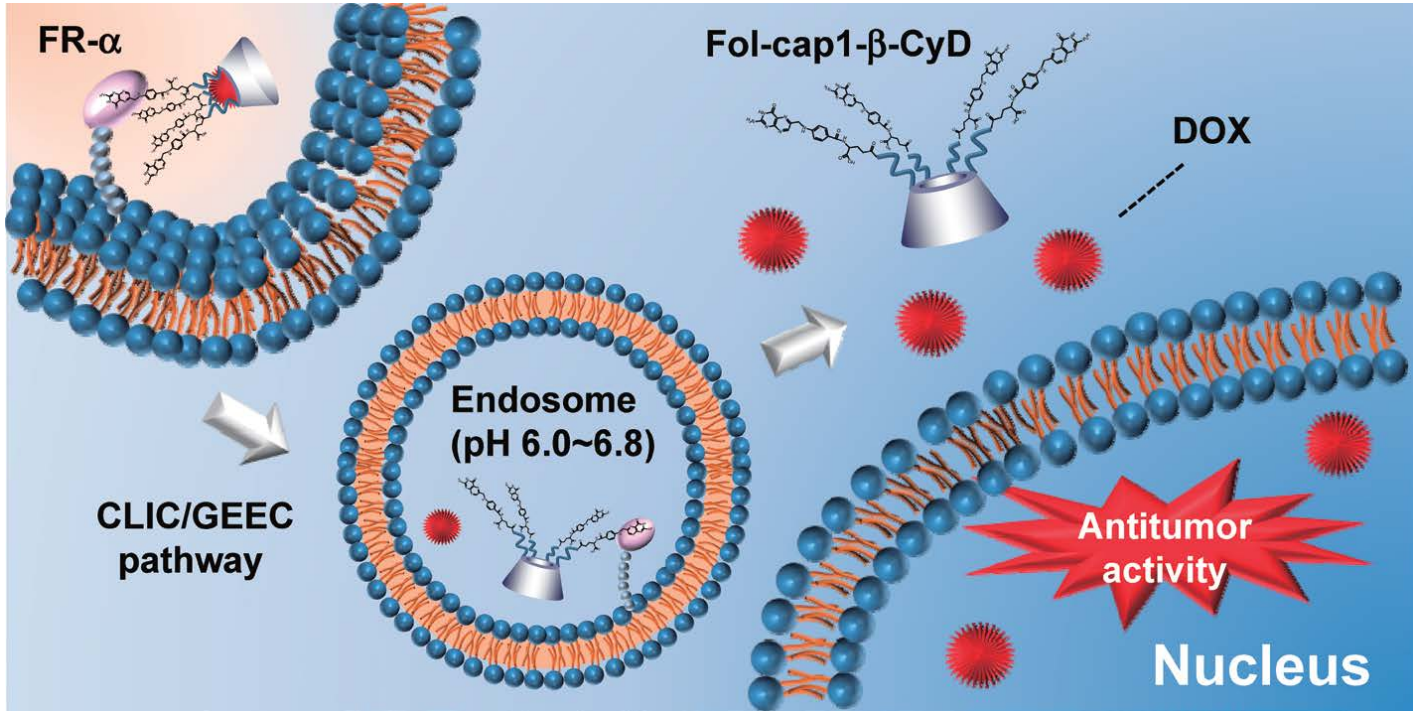


Ref: 22, 23

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

The stability constant of the DOX/Fol-c1-β-CyD complex showed **1.7×10⁶ M⁻¹** at **pH 7.3**. The data suggest that after intravenous injection of drug/CyD complexes having the extremely high stability constants more than 10^6 M^{-1}, the complexes can remain in the blood stream and distribute as the complex to the tumor tissues comparably to albumin-drug complexes. Interestingly, the stability constant of the DOX/Fol-c1-β-CyD complex decreased approximately by one-hundredth **at pH 6.8**, suggesting that the complex tends to dissociate in endolysosomes after endocytosis. Remarkably, Fol-c1-β-CyD increased antitumor activities of hydrophobic anticancer drugs such as *Paclitaxel (Taxol)* and *Vinblastine*, hydrophobic drugs, but not *5-Fluorouracil*, a hydrophilic drug. **These findings suggest that Fol-c1-β-CyD has the potential as a tumor-selective drug carrier.**

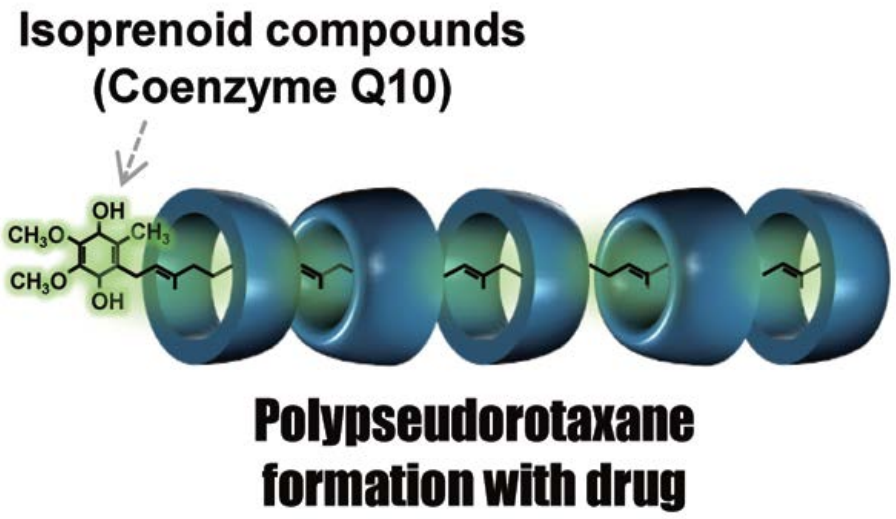
❖ Proposed Mechanism for Antitumor Effect of DOX Complex with Fol-c1-*β*-CyD



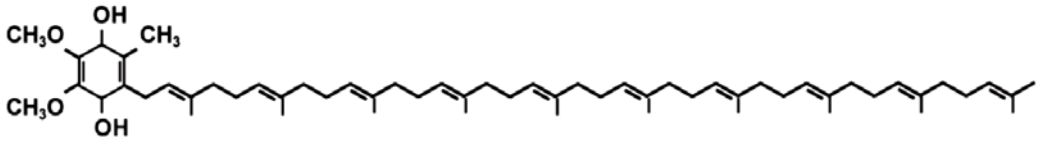
Ref: 24

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

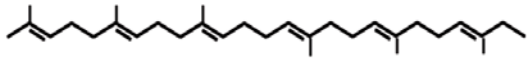
In the case of slender drugs, CyDs often form supramolecular complexes with the drugs. reported that isoprenoid compounds, such as *Coenzyme Q10 (CoQ10)*, *reduced CoQ10*, *Squalene*, *Tocotrienol* and *Teprenone,* form pseudorotaxanelike structures with a number of *β*-CyD or *γ*-CyD. Notably, solubility and photostability of the isoprenoid compounds were improved dramatically by pseudorotaxanelike supramolecular complexation.



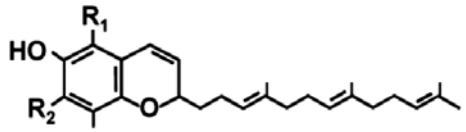
(A) Reduced CoQ10 (R-CoQ10)



(B) Squalene

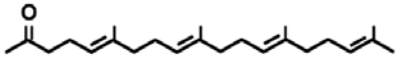


(C) Tocotrienol



Isomer	R_1	R_2
α	CH_3	CH_3
β	CH_3	H
γ	H	CH_3
δ	H	H

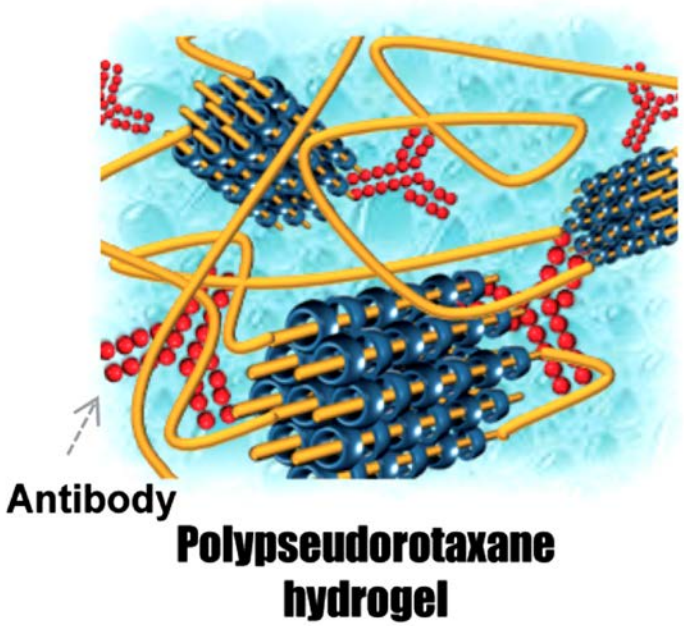
(D) Teprenone

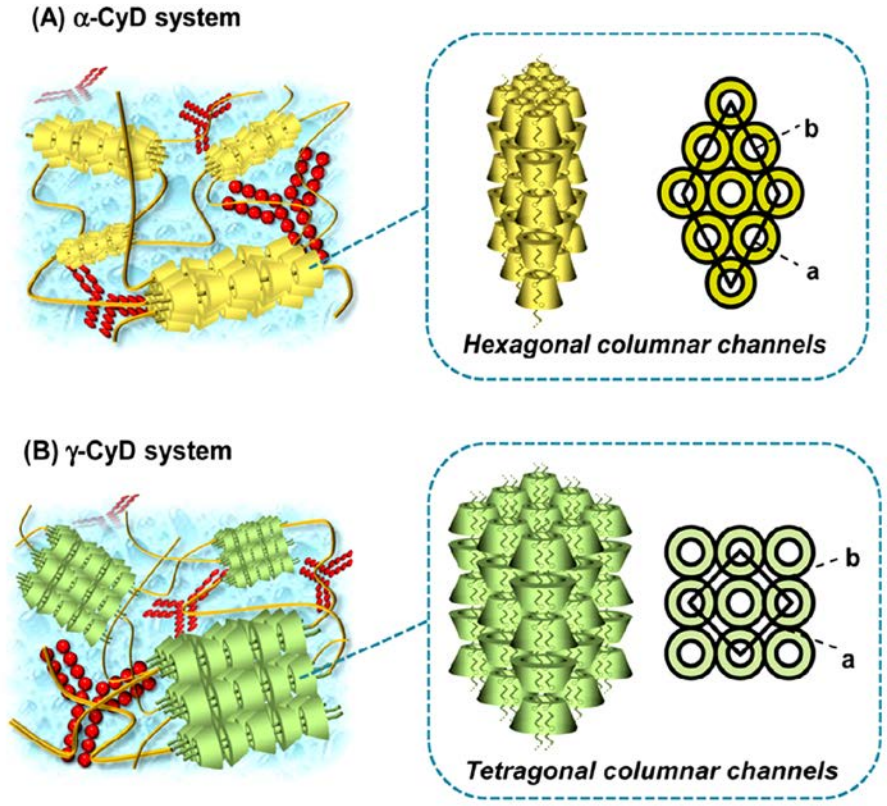


Ref: 25

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

Recently, APIs have been evolving from low-molecular weight drugs to peptides, proteins, and antibodies. However, proteins and antibodies often show low physicochemical stability during storage or transport or both. In this context, CyD/PEG polypseudorotaxanes markedly improved the stability of proteins and antibodies. The encapsulation of antibodies such as *Human Immunoglobulin G (IgG)*, *Omalizumab*, *Palivizumab*, *Panitumumab* and *Ranibizumab* in the hydrogels dramatically improved their shaking stability. Thus CyD/PEG polypseudorotaxanes work as a stabilizer for not only low-molecular weight drugs but also proteins and antibodies.



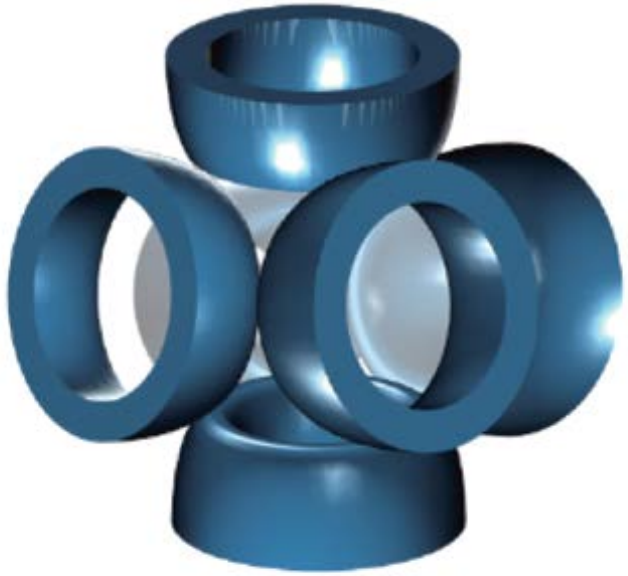


Ref: 26

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

Recently, a CyD-based metal-organic framework (CD-MOF) has been developed. CD-MOFs are prepared from *γ*-CyD in aqueous alcohol containing alkali metal salts. Eight-coordinate alkali metal cations orderly link the six *γ*-CyD molecules, resulting in a cubic structure. CD-MOFs are stable, porous, and capable of storing gases and small molecules within their pores. Currently, a considerable amount of research on CD-MOFs as pharmaceutical excipients is being aggressively performed.

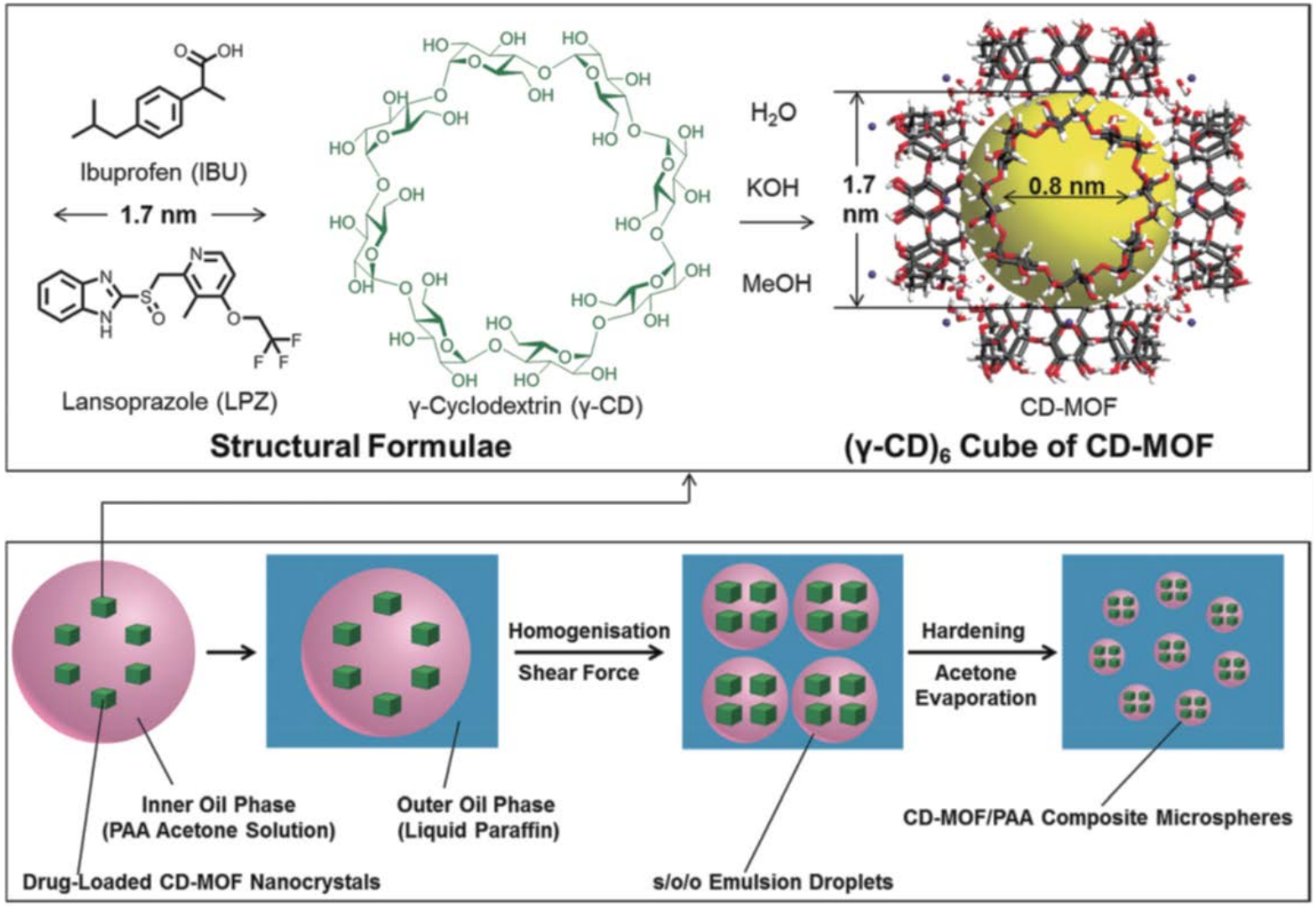
For instance, CD-MOF improved the stability of *Curcumin*, thermal stability of *Sucralose*, and bioavailability of *Ibuprofen*.



CD-MOF

Ref: 27

Cyclodextrin-Based Supramolecular Physical Pharmaceutics

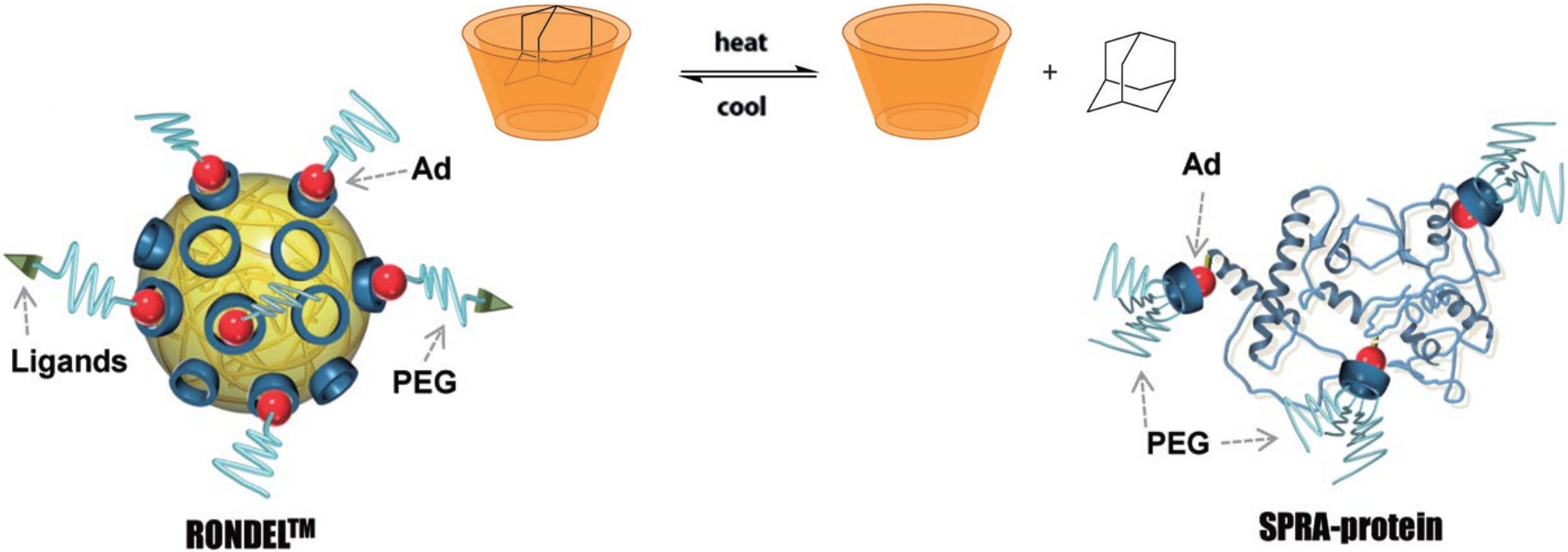


polyacrylic acid (PAA)

Ref: 27

Cyclodextrin-Based Supramolecular Drug Delivery

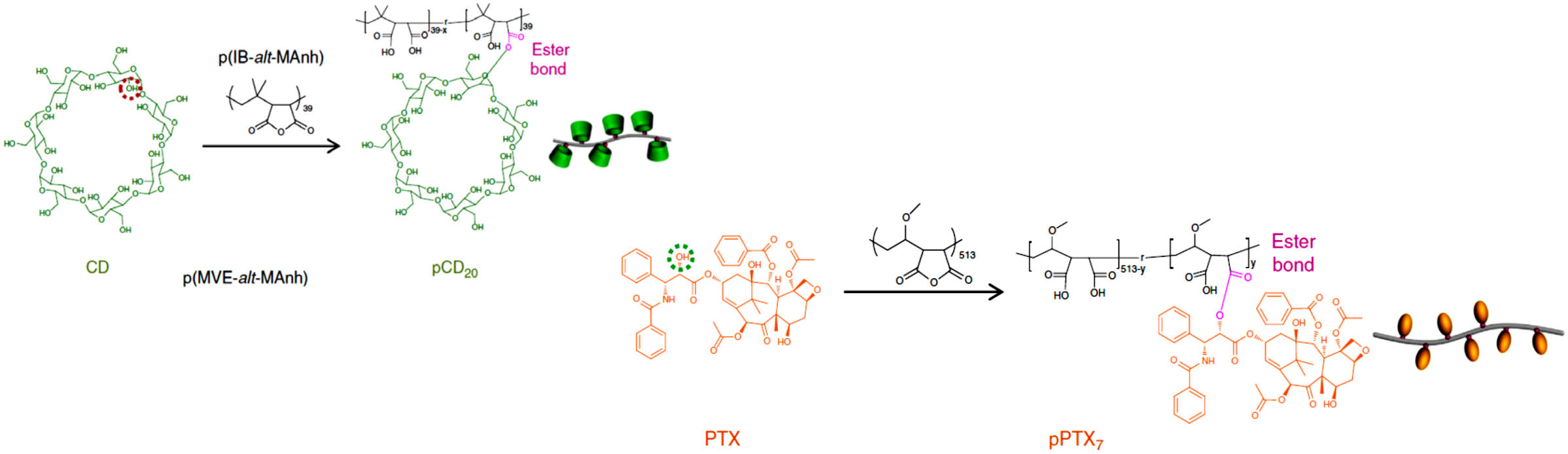
CyD-based supramolecular drug carriers are being aggressively developed. RONDEL™ is widely acknowledged as one of the most successful examples of CyD-based supramolecular drug carriers. RONDEL™ consists of small interfering RNA (siRNA), polyplex with cationic β-CyD polymer, Ad grafted PEG, and Ad-PEG-grafted transferrin. Transferrin, a tumor-targeting ligand, is grafted to the polyplex through the interaction between Ad and β-CyD. This strategy has been widely used by many researchers. recently developed a reversible PEGylation technology for protein drugs through host-guest interaction between Ad and β-CyD.



Ref: 1, 28

Cyclodextrin-Based Supramolecular Drug Delivery

As described above, weak interaction (Kc<10^4 M^{-1}) leads to drug dissociation in blood after injection. In this context, *Kim* and colleagues fabricated a supramolecular nanoparticle formed by multivalent host–guest interactions between a polymeric β-CyD and polymeric ***Paclitaxel***. The interaction between monomeric β-CyD and ***Paclitaxel*** is not strong, but the resulting supramolecular nanoparticle is stable because of the multivalent host-guest interactions. This nanoparticle accumulates in tumors by the EPR effect and shows antitumor activity *in vivo*.



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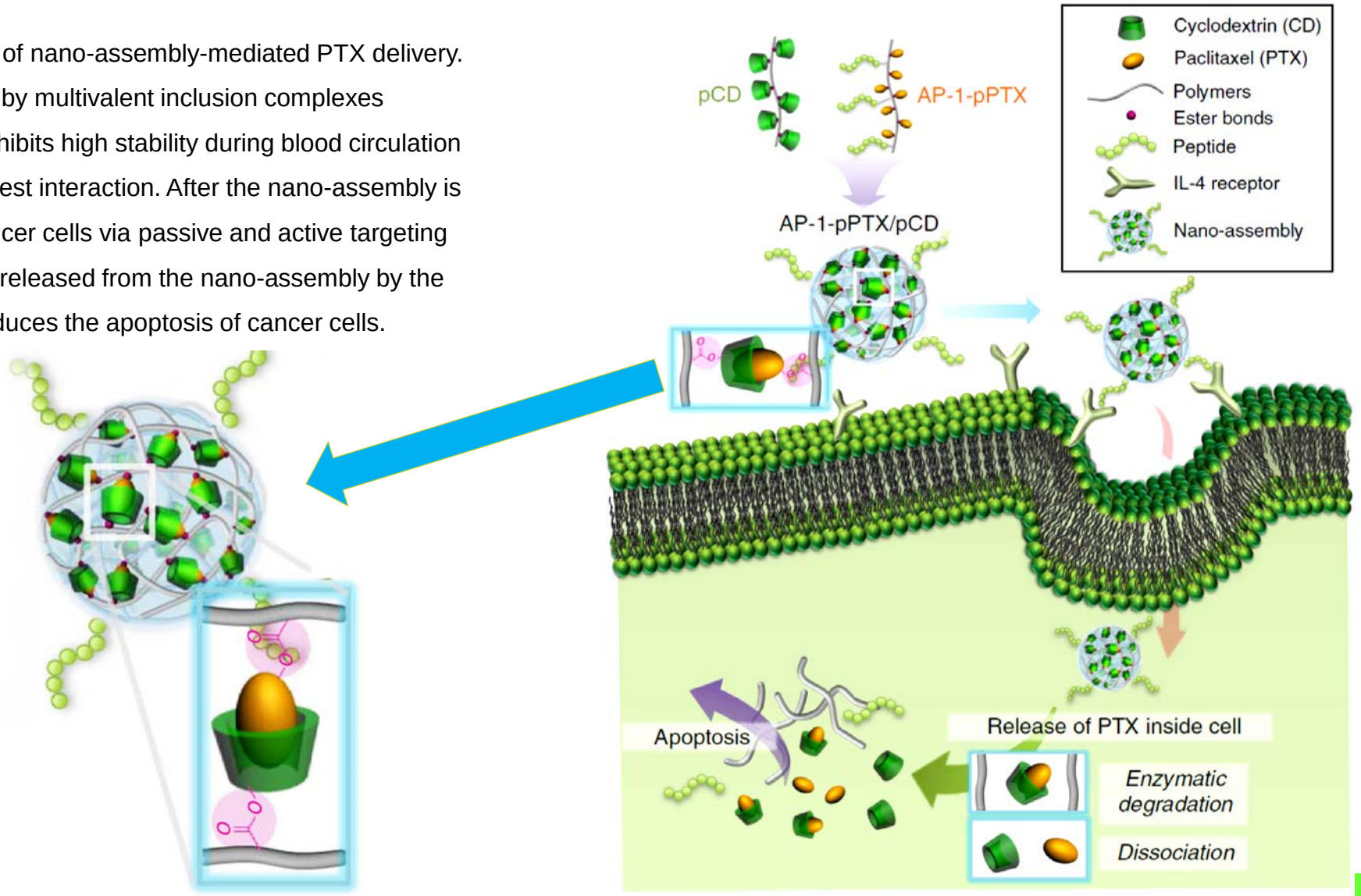
Cyclodextrin-Based Supramolecular Drug Delivery

❖ Schematic representation of nano-assembly-mediated PTX delivery. The nano-assembly is formed by multivalent inclusion complexes between pCD and pPTX. It exhibits high stability during blood circulation due to the multivalent host–guest interaction. After the nano-assembly is delivered into the targeted cancer cells via passive and active targeting mechanism, drug is efficiently released from the nano-assembly by the enzymatic degradation and induces the apoptosis of cancer cells.



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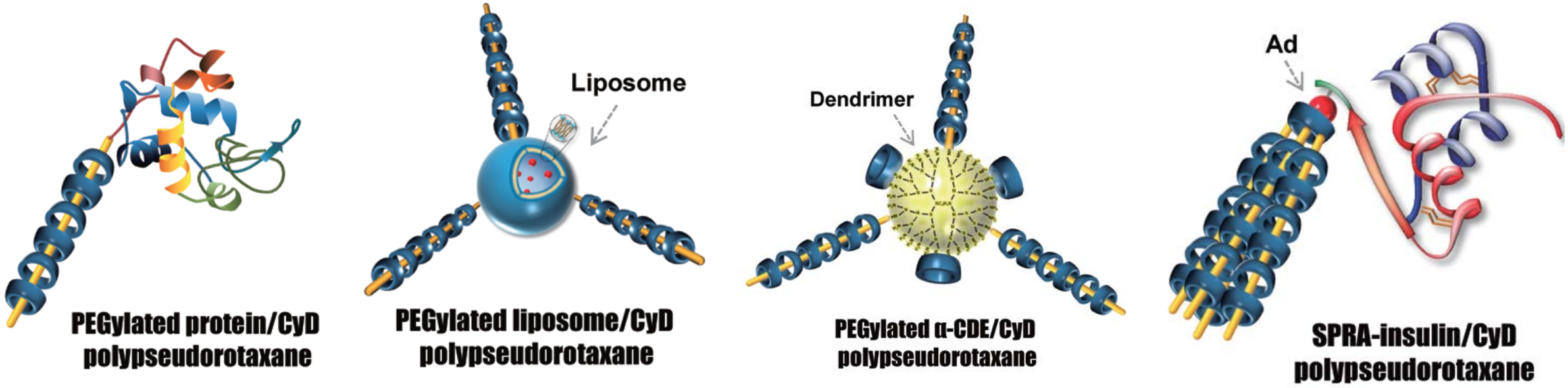
Cyclodextrin-Based Supramolecular Drug Delivery

Polypseudorotaxanes, a precursor of polyrotaxanes, are also useful as promising drug carriers. demonstrated that α-CyD and γ-CyD form water insoluble polypseudorotaxanes with covalently **PEGylated Insulin** (mw of PEG, 2 kDa) through inclusion complexation with one PEG chain and two PEG chains, respectively. The release of PEGylated insulin from the polypseudorotaxanes was sustained in vitro. Moreover, the blood insulin level and hypoglycemic effect of PEGylated insulin/γ-CyD polypseudorotaxane were markedly sustained after subcutaneous administration to rats. Importantly, PEGylated insulin alone did not show prolonged blood retention and hypoglycemic effect because of the low molecular weight of PEG (2 kDa).



Ref: 1

Toxicology of Cyclodextrin-Based Supermolecules

For CDs to be pharmaceutically useful, they must be biocompatible. CDs show resistance to degradation by human enzymes; CDs injected intravenously into humans are therefore essentially excreted intact via the kidney. However, bacterial and fungal enzymes (amylases) can degrade CDs. Ingested CDs can therefore be metabolized in the colon prior to excretion.

The toxicities of CDs are dependent on their route of administration. For example, the dose that causes 50% death (LD50) values of α-, β- and γ-CD administered intravenously into mice are approximately 1.0 g per kg, 0.79 g per kg and more than 4.0 g per kg, respectively. β-CD has an affinity for cholesterol and can extract it and other lipid membrane components from cells. At sufficiently high concentrations, β-CD can cause haemolysis of erythrocytes.

Additionally, parenteral administration of β-CD is not possible because of its poor solubility (which leads to microcrystalline precipitation in the kidney), as well as the fact that it forms complexes with cholesterol that accumulate in the kidney and produce renal tubule damage.

Ref: 2

Toxicology of Cyclodextrin-Based Supermolecules

CyDs have been used as pharmaceutical excipients because of their high safety. However, as described above CyDs occasionally show toxicity in the lung, bone, ears and kidney. In contrast to the abundant safety data of CyDs, very few data are available on the safety of CyD-based supermolecules.

Tamura and Yui reported that HEE-*β*-CyD polyrotaxane shows markedly lower hemolytic activity and cytotoxicity than DM-*β*-CyD and HP-*β*-CyD because the ***axile molecule occupies*** the CyD cavity.

Collins et al. investigated the acute toxicity of HP-*β*-CyD polyrotaxanes with PEG-PPGPEGs. The polyrotaxanes were intravenously administered twice over 3 weeks to male Balb/c mice. After administration, negligible body weight change was observed, indicating that the polyrotaxanes did not exhibit acute toxicity in mice.

Moreover, blood chemistry parameters, such as blood urea nitrogen (BUN), alkaline phosphatase (ALKP), alanine transaminase (ALT), and blood CO_2 did not change after administration of polyrotaxanes, suggesting the absence of acute toxicity in the kidney, liver, and lung. Furthermore, administration of polyrotaxanes did not stimulate IgG production, suggesting their low immunogenicity.

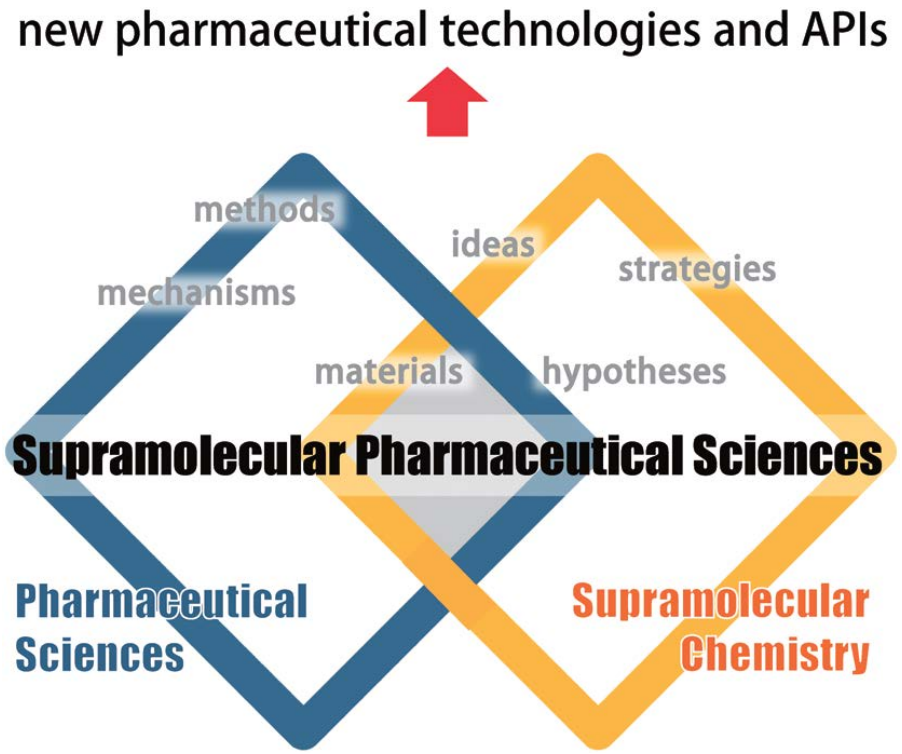
Ref: 1

Conclusion

In this review article, we describe various CyD-based supermolecules and their use as biomaterials, pharmaceutical excipients, drug carriers, and APIs. Additionally, we discussed the chemistry, pharmacokinetics, and toxicology of CyD-based supermolecules. Currently, drugs are undergoing evolution from low-molecular weight synthetics to peptides, proteins, and antibodies. Moreover, genes, oligonucleotides,

cells, and machines are promising APIs for next-generation.

To improve the pharmaceutical properties of these APIs, advanced pharmaceutical technologies are needed. We believe that the incorporation of supramolecular chemistry into pharmaceutical sciences can create advanced pharmaceutical technologies. Indeed, as described in this review, PEGylation of proteins through supramolecular chemistry (i.e. SPRA technology) renders advanced pharmaceutical benefits over conventional PEGylation (i.e. covalent bond). In addition, modification of supermolecules (i.e. polypseudorotaxane) improves the pharmaceutical properties of proteins compared to conventional modification with macromolecules (i.e. PEG). Thus supramolecular chemistry as an alternative to chemistry and supermolecules as an alternative to macromolecules may help create advanced technologies. Furthermore, CyD-based supermolecules work as APIs by themselves, facilitating the development of new kinds of drugs. In conclusion, fusion of supramolecular chemistry and pharmaceutical sciences, namely supramolecular pharmaceutical sciences, could be an important domain to develop new pharmaceutical sciences.



Ref: 1

REFERENCES

1- Higashi, T., Iohara, D., Motoyama, K., & Arima, H. (2018). Supramolecular Pharmaceutical Sciences: A Novel Concept Combining Pharmaceutical Sciences and Supramolecular Chemistry with a Focus on Cyclodextrin-Based Supermolecules. Chemical and Pharmaceutical Bulletin, 66(3), 207-216.

2- Webber, M. J., & Langer, R. (2017). Drug delivery by supramolecular design. Chemical Society Reviews, 46(21), 6600-6620.

3- Ma, X., & Zhao, Y. (2014). Biomedical applications of supramolecular systems based on host–guest interactions. Chemical reviews, 115(15), 7794-7839.

4- Ogoshi, T., & Yamagishi, T. A. (2014). Pillar [5]-and pillar [6] arene-based supramolecular assemblies built by using their cavity-size-dependent host–guest interactions. Chemical Communications, 50(37), 4776-4787.

5- Strutt, N. L., Zhang, H., Schneebeli, S. T., & Stoddart, J. F. (2014). Functionalizing pillar [n] arenes. Accounts of chemical research, 47(8), 2631-2642.

6- Kou, Y., Cao, D., Tao, H., Wang, L., Liang, J., Chen, Z., & Meier, H. (2013). Synthesis and inclusion properties of pillar [n] arenes. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 77(1-4), 279-289.

7- Zhou, Y., Li, H., & Yang, Y. W. (2015). Controlled drug delivery systems based on calixarenes. Chinese Chemical Letters, 26(7), 825-828.

8- Wheate, N. J., Abbott, G. M., Tate, R. J., Clements, C. J., Edrada-Ebel, R., & Johnston, B. F. (2009). Side-on binding of p-sulphonatocalix [4] arene to the dinuclear platinum complex trans-[{PtCl (NH3) 2} 2μ-dpzm] 2+ and its implications for anticancer drug delivery. Journal of inorganic biochemistry, 103(3), 448-454.

9- Gokel, G. W., Leevy, W. M., & Weber, M. E. (2004). Crown ethers: sensors for ions and molecular scaffolds for materials and biological models. Chemical reviews, 104(5), 2723-2750.

REFERENCES

10- Day, A., Arnold, A. P., Blanch, R. J., & Snushall, B. (2001). Controlling factors in the synthesis of cucurbituril and its homologues. The Journal of organic chemistry, 66(24), 8094-8100.

11- Assaf, K. I., & Nau, W. M. (2015). Cucurbiturils: from synthesis to high-affinity binding and catalysis. Chemical Society Reviews, 44(2), 394-418.

12- Davis, M. E., & Brewster, M. E. (2004). Cyclodextrin-based pharmaceutics: past, present and future. Nature reviews Drug discovery, 3(12), 1023.

13- Nakazono, K., Takashima, T., Arai, T., Koyama, Y., & Takata, T. (2009). High-yield one-pot synthesis of permethylated α-cyclodextrin-based polyrotaxane in hydrocarbon solvent through an efficient heterogeneous reaction. Macromolecules, 43(2), 691-696.

14- Mondjinou, Y. A., Hyun, S. H., Xiong, M., Collins, C. J., Thong, P. L., & Thompson, D. H. (2015). Impact of mixed β-cyclodextrin ratios on Pluronic rotaxanation efficiency and product solubility. ACS applied materials & interfaces, 7(43), 23831-23836.

15- Higashi, T., Li, J., Song, X., Zhu, J., Taniyoshi, M., Hirayama, F., ... & Arima, H. (2016). Thermoresponsive formation of dimethyl cyclodextrin polypseudorotaxanes and subsequent one-pot synthesis of polyrotaxanes. ACS Macro Letters, 5(2), 158-162.

16- Collins, C. J., Mondjinou, Y., Loren, B., Torregrosa-Allen, S., Simmons, C. J., Elzey, B. D., ... & Thompson, D. (2016). Influence of molecular structure on the in vivo performance of flexible rod polyrotaxanes. Biomacromolecules, 17(9), 2777-2786.

17- Stella, V. J., Rao, V. M., Zannou, E. A., & Zia, V. (1999). Mechanisms of drug release from cyclodextrin complexes. Advanced drug delivery reviews, 36(1), 3-16.

18- Kurkov, S. V., Madden, D. E., Carr, D., & Loftsson, T. (2012). The effect of parenterally administered cyclodextrins on the pharmacokinetics of coadministered drugs. Journal of pharmaceutical sciences, 101(12), 4402-4408.

REFERENCES

19- Mondjinou, Y. A., McCauliff, L. A., Kulkarni, A., Paul, L., Hyun, S. H., Zhang, Z., ... & Thompson, D. H. (2013). Synthesis of 2-hydroxypropyl-β-cyclodextrin/pluronic-based polyrotaxanes via heterogeneous reaction as potential Niemann-Pick type C therapeutics. Biomacromolecules, 14(12), 4189-4197.

20- Higashi, K., Waraya, H., Lin, L. K., Namiki, S., Ogawa, M., Limwikrant, W., ... & Moribe, K. (2014). Application of intermolecular spaces between polyethylene glycol/γ-cyclodextrin-polypseudorotaxanes as a host for various guest drugs. Crystal Growth & Design, 14(6), 2773-2781.

21- Ogawa, M., Higashi, K., Namiki, S., Liu, N., Ueda, K., Limwikrant, W., ... & Moribe, K. (2017). Solid-phase mediated methodology to incorporate drug into intermolecular spaces of cyclodextrin columns in polyethylene glycol/cyclodextrin-polypseudorotaxanes by cogrinding and subsequent heating. Crystal Growth & Design, 17(3), 1055-1068.

22- Okamatsu, A., Motoyama, K., Onodera, R., Higashi, T., Koshigoe, T., Shimada, Y., ... & Arima, H. (2013). Folate-appended β-cyclodextrin as a promising tumor targeting carrier for antitumor drugs in vitro and in vivo. Bioconjugate chemistry, 24(4), 724-733.

23- Caliceti, P., Salmaso, S., Semenzato, A., Carofiglio, T., Fornasier, R., Fermeglia, M., ... & Pricl, S. (2003). Synthesis and physicochemical characterization of folate− cyclodextrin bioconjugate for active drug delivery. Bioconjugate chemistry, 14(5), 899-908.

24- Arima, H., Motoyama, K., & Higashi, T. (2017). Potential use of cyclodextrins as drug carriers and active pharmaceutical ingredients. Chemical and Pharmaceutical Bulletin, 65(4), 341-348.

REFERENCES

25- Higashi, T., Tanaka, H., Yoshimatsu, A., Ikeda, H., Arima, K., Honjo, M., ... & Arima, H. (2016). Improvement of Pharmaceutical Properties of Isoprenoid Compounds through the Formation of Cyclodextrin Pseudorotaxane-Like Supramolecules. Chemical and Pharmaceutical Bulletin, 64(4), 340-345.

26- Ohshita, N., Tajima, A., Higashi, T., Motoyama, K., Koyama, S., Iibuchi, R., ... & Arima, H. (2016). Improvement of physicochemical stability of highly-concentrated antibodies using cyclodextrin polypseudorotaxane hydrogels. Asian Journal of Pharmaceutical Sciences, 1(11), 221-222.

27- Li, H., Lv, N., Li, X., Liu, B., Feng, J., Ren, X., ... & Zhang, J. (2017). Composite CD-MOF nanocrystals-containing microspheres for sustained drug delivery. Nanoscale, 9(22), 7454-7463.

28- Schmidt, B. V., & Barner-Kowollik, C. (2017). Dynamic Macromolecular Material Design—The Versatility of Cyclodextrin-Based Host–Guest Chemistry. Angewandte Chemie International Edition, 56(29), 8350-8369

29- Namgung, R., Lee, Y. M., Kim, J., Jang, Y., Lee, B. H., Kim, I. S., ... & Kim, W. J. (2014). Poly-cyclodextrin and poly-paclitaxel nano-assembly for anticancer therapy. Nature communications, 5, 3702.

30- Barbera, L., Franco, D., De Plano, L. M., Gattuso, G., Guglielmino, S. P., Lentini, G., ... & Puntoriero, F. (2017). A water-soluble pillar [5] arene as a new carrier for an old drug. Organic & biomolecular chemistry, 15(15), 3192-3195.

پایان

سپاسگزارم


زندگی زیباست ای زیبا پسند
زنده پرستان به زیبایی رسند
آنقدر زیباست این بی بازگشت
کز برایش می توان از جان گذشت
ه. ا. سایه